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1KSG **Complex of Arl2 and PDE delta, Crystal Form 1**

Characteristics **Release Date:** 08-May-2002 **Exp. Method:** X Ray Diffraction
Resolution: 2.30 Å

Classification **Signaling Protein/hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Arf Like Protein 2 **Mutation:** S33L **Mol. Id:** 2 **Molecule:** Retinal Rod Rhodopsin Sensitive Cgmp 3' 5' Cyclic Phosphodiesterase Delta Subunit

Authors **Hanzal-Bayer, M., Renault, L., Roversi, P., Wittinghofer, A., Hillig, R.C.**

1KSH **Complex of Arl2 and PDE delta, Crystal Form 2 (native)**

Characteristics **Release Date:** 08-May-2002 **Exp. Method:** X Ray Diffraction
Resolution: 1.80 Å

Classification **Signaling Protein/hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Arf Like Protein 2 **Mutation:** S33L **Mol. Id:** 2 **Molecule:** Retinal Rod Rhodopsin Sensitive Cgmp 3' 5' Cyclic Phosphodiesterase Delta Subunit

Authors **Hanzal-Bayer, M., Renault, L., Roversi, P., Wittinghofer, A., Hillig, R.C.**

1KSJ **Complex of Arl2 and PDE delta, Crystal Form 2 (SeMet)**

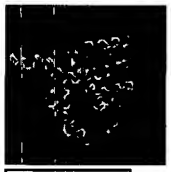
Characteristics **Release Date:** 08-May-2002 **Exp. Method:** X Ray Diffraction
Resolution: 2.60 Å

Classification **Signaling Protein/hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Arf Like Protein 2 **Mutation:** S33L **Mol. Id:** 2 **Molecule:** Retinal Rod Rhodopsin Sensitive Cgmp 3' 5' Cyclic Phosphodiesterase Delta Subunit

Authors **Hanzal-Bayer, M., Renault, L., Roversi, P., Wittinghofer, A., Hillig, R.C.**

☑ 1TAZ



Catalytic Domain Of Human Phosphodiesterase 1B

Characteristics **Release Date:** 03-Aug-2004 **Exp. Method:** X Ray Diffraction

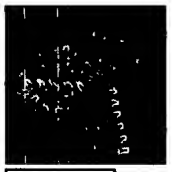
Resolution: 1.77 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Calcium/calmodulin Dependent 3' 5' Cyclic Nucleotide Phosphodiesterase 1b **Fragment:** Catal Domain

Authors **Zhang, K.Y.J., Card, G.L., Suzuki, Y., Artis, D.R., Fong, D., Gillette, S., Hsieh, D., Neiman, J., West, B.L., Zhang, C., Milburn, M.V., Kim, S.-H., Schlessinger, J., Bollag, G.**

☑ 1XP0



Catalytic Domain Of Human Phosphodiesterase 5A In Complex With Vardenafil

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 1.79 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain of Human Phosphodiesterase 5a

Authors **Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.**

☑ 1Z1L

The Crystal Structure of the Phosphodiesterase 2A Catalytic Domain

Characteristics **Release Date:** 21-Jun-2005 **Exp. Method:** X Ray Diffraction

Resolution: 1.70 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Dependent 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain Residues 578 9

Authors **Iffland, A., Kohls, D., Low, S., Luan, J., Zhang, Y., Kothe, M., Cao, Q., Kamath, A.V., Ding, Y.H., Ellenberger, T.**

☑ 1KN4

CATALYTIC ANTIBODY D2.3 COMPLEX

Characteristics **Release Date:** 13-Mar-2002 **Exp. Method:** X Ray Diffraction

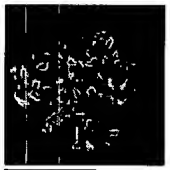
Resolution: 1.90 Å

Classification **Immune System**

Compound **Mol. Id:** 1 **Molecule:** Ig Antibody D2.3 (light Chain) **Mol. Id:** 2 **Molecule:** Ig Antibody D2.3 (heavy Chain)

Authors **D`Souza, L.J., Gigant, B., Knossow, M., Green, B.S.**

☑ 1RKP



Crystal structure of PDE5A1-IBMX

Characteristics **Release Date:** 30-Mar-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.05 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain (residues 535 860

Mutation: I778L

Authors **Huai, Q., Liu, Y., Francis, S.H., Corbin, J.D., Ke, H.**

☑ 1T9R

Catalytic Domain Of Human Phosphodiesterase 5A

Characteristics **Release Date:** 03-Aug-2004 **Exp. Method:** X Ray Diffraction

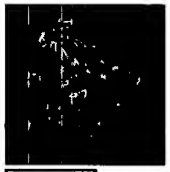
Resolution: 2.10 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain

Authors **Zhang, K.Y.J., Card, G.L., Suzuki, Y., Artis, D.R., Fong, D., Gillette, S., Hsieh, D., Neiman, J., West, B.L., Zhang, C., Milburn, M.V., Kim, S.-H., Schlessinger, J., Bollag, G.**

☑ 2H40



Crystal structure of the catalytic domain of unliganded PDE5

Characteristics **Release Date:** 06-Jun-2006 **Exp. Method:** X Ray Diffraction

Resolution: 1.85 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain Residues 535 860

Authors **Wang, H., Liu, Y., Huai, Q., Cai, J., Zoraghi, R., Francis, S.H., Corbin, J.D., Robinson, H., X Z., Lin, G., Ke, H.**

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2H44

Crystal structure of PDE5A1 in complex with icarisid II

Characteristics **Release Date:** 06-Jun-2006 **Exp. Method:** X Ray Diffraction

Resolution: 1.80 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain Residues 535 860

Authors **Wang, H., Liu, Y., Huai, Q., Cai, J., Zoraghi, R., Francis, S.H., Corbin, J.D., Robinson, H., Xia, Z., Lin, G., Ke, H.**

1XOZ

Catalytic Domain Of Human Phosphodiesterase 5A In Complex With Tadalafil

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

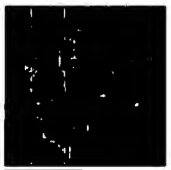
Resolution: 1.37 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain of Human Phosphodiesterase 5a

Authors **Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger J., Zhang, K.Y.J.**

1FZQ



CRYSTAL STRUCTURE OF MURINE ARL3-GDP

Characteristics **Release Date:** 06-Dec-2000 **Exp. Method:** X Ray Diffraction

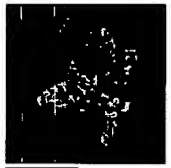
Resolution: 1.70 Å

Classification **Signaling Protein**

Compound **Mol. Id:** 1 **Molecule:** Adp Ribosylation Factor Like Protein 3

Authors **Hillig, R.C., Hanzal-Bayer, M., Linari, M., Becker, J., Wittinghofer, A., Renault, L.**

☑ 1TBF



Catalytic Domain Of Human Phosphodiesterase 5A in Complex with Sildenafil

Characteristics **Release Date:** 03-Aug-2004 **Exp. Method:** X Ray Diffraction

Resolution: 1.30 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain

Authors **Zhang, K.Y.J., Card, G.L., Suzuki, Y., Artis, D.R., Fong, D., Gillette, S., Hsieh, D., Neiman, J., West, B.L., Zhang, C., Milburn, M.V., Kim, S.-H., Schlessinger, J., Bollag, G.**

☑ 1X2A

Crystal Structure of e.coli AspAT complexed with N-phosphopyridoxyl-D-glutamic acid

Characteristics **Release Date:** 14-Jun-2005 **Exp. Method:** X Ray Diffraction

Resolution: 2.20 Å

Classification **Transferase**

Compound **Mol. Id:** 1 **Molecule:** Aspartate Aminotransferase

Authors **Islam, M.M., Goto, M., Miyahara, I., Ikushiro, H., Hirotsu, K., Hayashi, H.**

☑ 2H42

Crystal structure of PDE5 in complex with sildenafil

Characteristics **Release Date:** 06-Jun-2006 **Exp. Method:** X Ray Diffraction

Resolution: 2.30 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain Residues 535 860

Authors **Wang, H., Liu, Y., Huai, Q., Cai, J., Zoraghi, R., Francis, S.H., Corbin, J.D., Robinson, H., Z., Lin, G., Ke, H.**

☑ 1UHO

Crystal structure of Human Phosphodiesterase 5 complexed with Vardenafil(Levitra)

Characteristics **Release Date:** 09-Jul-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.50 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain

Authors **Sung, B.-J., Hwang, K.Y., Jeon, Y.H., Lee, J.I., Heo, Y.-S., Kim, J.H., Moon, J., Yoon, J.M., Hyun, Y.-L., Kim, E., Eum, S.J., Park, S.-Y., Lee, J.-O., Lee, T.G., Ro, S., Cho, J.M.**

☑ 1XOS

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With Sildenafil

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.28 Å

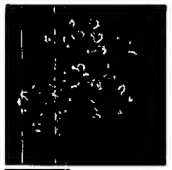
Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors **Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.**

☑ **1ZKL**

Multiple Determinants for Inhibitor Selectivity of Cyclic Nucleotide Phosphodiesterases



Characteristics **Release Date:** 05-Jul-2005 **Exp. Method:** X Ray Diffraction

Resolution: 1.67 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** High Affinity Camp Specific 3' 5' Cyclic Phosphodiesterase 7a **Fragment:** Catalytic Domain (1 482)

Authors **Wang, H., Liu, Y., Chen, Y., Robinson, H., Ke, H.**

☑ **1FQJ**

CRYSTAL STRUCTURE OF THE HETEROTRIMERIC COMPLEX OF THE RGS DOMAIN OF RGS9, THE GAMMA SUBUNIT OF PHOSPHODIESTERASE AND THE GT/I1 CHIMERA ALPHA SUBUNIT [(RGS9)-(PDEGAMMA)-(GT/I1ALPHA)-(GDP)-(ALF4-)-(MG2+)]

Characteristics **Release Date:** 28-Feb-2001 **Exp. Method:** X Ray Diffraction

Resolution: 2.02 Å

Classification **Signaling Protein**

Compound **Mol. Id:** 1 **Molecule:** Chimera of Guanine Nucleotide Binding Protein G(t) Alpha 1 Subunit and Guanine Nucleotide Binding Protein G(i) Alpha 1 Subunit **Mol. Id:** 2 **Molecule:** Regulator of G Protein Signaling 9 **Fragment:** Rgs Don (residues 276 422) **Mol. Id:** 3 **Molecule:** Retinal Rod Rhodopsin Sensitive Cgmp 3' 5' Cyclic Phosphodiesterase Gan Subunit **Fragment:** Pdegamma (residues 46 87)

Authors **Slep, K.C., Kercher, M.A., He, W., Cowan, C.W., Wensel, T.G., Sigler, P.B.**

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☑ **1T9S**

Catalytic Domain Of Human Phosphodiesterase 5A in Complex with GMP

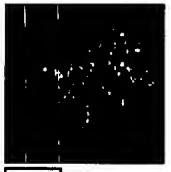
Characteristics **Release Date:** 03-Aug-2004 **Exp. Method:** X Ray Diffraction
Resolution: 2.00 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase **Fragment:** Catalytic Domain

Authors **Zhang, K.Y.J., Card, G.L., Suzuki, Y., Artis, D.R., Fong, D., Gillette, S., Hsieh, D., Neiman, J., West, B.L., Zhang, C., Milburn, M.V., Kim, S.-H., Schlessinger, J., Bollag, G.**

☑ **1SO2**



CATALYTIC DOMAIN OF HUMAN PHOSPHODIESTERASE 3B In COMPLEX WITH A DIHYDROPYRIDAZINE INHIBITOR

Characteristics **Release Date:** 11-May-2004 **Exp. Method:** X Ray Diffraction
Resolution: 2.40 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Inhibited 3' 5' Cyclic Phosphodiesterase B **Fragment:** Catalytic Domain Residues 654 1073

Authors **Scapin, G., Patel, S.B., Chung, C., Varnerin, J.P., Edmondson, S.D., Mastracchio, A., Parm E.R., Singh, S.B., Becker, J.W., Van Der Ploeg, L.H., Tota, M.R.**

☑ **1RO6**

Crystal structure of PDE4B2B complexed with Rolipram (R & S)

Characteristics **Release Date:** 07-Dec-2004 **Exp. Method:** X Ray Diffraction
Resolution: 2.00 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain
Mutation: S487A, S489A

Authors **Xu, R.X., Rocque, W.J., Lambert, M.H., Vanderwall, D.E., Luther, M.A., Nolte, R.T.**

☑ 1RO9

CRYSTAL STRUCTURES OF THE CATALYTIC DOMAIN OF PHOSPHODIESTERASE 4B2B COMPLEXED WITH 8-Br-AMP

Characteristics **Release Date:** 07-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.13 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain

Mutation: S487A, S489A

Authors **Xu, R.X., Rocque, W.J., Lambert, M.H., Vanderwall, D.E., Luther, M.A., Nolte, R.T.**

☑ 1ROR

CRYSTAL STRUCTURES OF THE CATALYTIC DOMAIN OF PHOSPHODIESTERASE 4B2B COMPLEXED WITH AMP

Characteristics **Release Date:** 07-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.00 Å

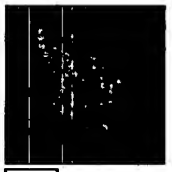
Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain

Mutation: S487A, S489A

Authors **Xu, R.X., Rocque, W.J., Lambert, M.H., Vanderwall, D.E., Luther, M.A., Nolte, R.T.**

☑ 1TBM



Crystal structure of phosphodiesterase 9 shows orientation variation of inhibitor IBMX binding

Characteristics **Release Date:** 06-Jul-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.23 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Cgmp Phosphodiesterase A2 **Fragment:** Catalytic Domain

Authors **Huai, Q., Wang, H., Zhang, W., Colman, R.W., Robinson, H., Ke, H.**

☑ 1XMU

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With Roflumilast

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.30 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b **Mol. Id:** 2 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad,

Authors M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.

☑ 1XMY

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With (R)-Rolipram

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.40 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b **Mol. Id:** 2 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.

☑ 1XN0

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With (R,S)-Rolipram

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.31 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.

☑ 1XOQ

Catalytic Domain Of Human Phosphodiesterase 4D In Complex With Roflumilast

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 1.83 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4d **Fragment:** Catalytic Domain of Human Phosphodiesterase 4d

Authors Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.

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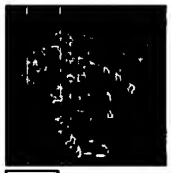
☑ **1XOT**



Catalytic Domain Of Human Phosphodiesterase 4B In Complex With Vardenafil

Characteristics **Release Date:** 14-Dec-2004 **Exp. Method:** X Ray Diffraction

Resolution: 2.34 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors **Card, G.L., England, B.P., Suzuki, Y., Fong, D., Powell, B., Lee, B., Luu, C., Tabrizizad, M., Gillette, S., Ibrahim, P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessing J., Zhang, K.Y.J.**

☑ **1Y2B**

Catalytic Domain Of Human Phosphodiesterase 4D In Complex With 3,5-dimethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Characteristics **Release Date:** 01-Mar-2005 **Exp. Method:** X Ray Diffraction

Resolution: 1.40 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4d **Fragment:** Catalytic Domain of Human Phosphodiesterase 4d

Authors **Card, G.L., Blasdel, L., England, B.P., Zhang, C., Suzuki, Y., Gillette, S., Fong, D., Ibrahim P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.**

☑ **1Y2C**

Catalytic Domain Of Human Phosphodiesterase 4D In Complex With 3,5-dimethyl-1-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester

Characteristics **Release Date:** 01-Mar-2005 **Exp. Method:** X Ray Diffraction

Resolution: 1.67 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4d **Fragment:** Catalytic Domain of Human

Phosphodiesterase 4d

Authors **Card, G.L., Blasdel, L., England, B.P., Zhang, C., Suzuki, Y., Gillette, S., Fong, D., Ibrahim P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.**

☑ **1Y2E**

Catalytic Domain Of Human Phosphodiesterase 4D In Complex With 1-(4-amino-phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Characteristics **Release Date:** 01-Mar-2005 **Exp. Method:** X Ray Diffraction

Resolution: 2.10 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4d **Fragment:** Catalytic Domain of Human Phosphodiesterase 4d

Authors **Card, G.L., Blasdel, L., England, B.P., Zhang, C., Suzuki, Y., Gillette, S., Fong, D., Ibrahim P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.**

☑ **1Y2H**

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With 1-(2-chloro-phenyl)-3,5-dimethyl-1H-pyrazole-4-carboxylic acid ethyl ester

Characteristics **Release Date:** 01-Mar-2005 **Exp. Method:** X Ray Diffraction

Resolution: 2.40 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors **Card, G.L., Blasdel, L., England, B.P., Zhang, C., Suzuki, Y., Gillette, S., Fong, D., Ibrahim P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.**

☑ **1Y2J**

Catalytic Domain Of Human Phosphodiesterase 4B In Complex With 3,5-dimethyl-1-(3-nitro-phenyl)-1H-pyrazole-4-carboxylic acid ethyl ester

Characteristics **Release Date:** 01-Mar-2005 **Exp. Method:** X Ray Diffraction

Resolution: 2.55 Å

Classification **Hydrolase**

Compound **Mol. Id:** 1 **Molecule:** Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain of Human Phosphodiesterase 4b

Authors **Card, G.L., Blasdel, L., England, B.P., Zhang, C., Suzuki, Y., Gillette, S., Fong, D., Ibrahim P.N., Artis, D.R., Bollag, G., Milburn, M.V., Kim, S.-H., Schlessinger, J., Zhang, K.Y.J.**

☑ **2CHM**

CRYSTAL STRUCTURE OF N2 SUBSTITUTED PYRAZOLO PYRIMIDINONES-A FLIPPED BINDING MODE IN PDE5

Characteristics **Release Date:** 08-Jun-2006 **Exp. Method:** X Ray Diffraction

Resolution: 1.60 Å

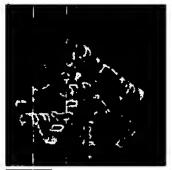
Classification **Hydrolase**

Compound **Mol. Id: 1 Molecule:** Cgmp Specific 3' 5' Cyclic Phosphodiesterase Camp Specific 3' 5' Cyclic Phosphodiesterase 4b **Fragment:** Catalytic Domain Residues (residues 534 858 with Subdomain Replaced with Pde4 Subdomain)

Authors **Allerton, C.M.N., Barber, C.G., Beaumont, K.C., Brown, D.G., Cole, S.M., Ellis, D., Lane, C.A.L., Maw, G.N., Mount, N.M., Rawson, D.J., Robinson, C.M., Street, S.D.A., Summerhill, N.W.**

☑ **1F0J**

CATALYTIC DOMAIN OF HUMAN PHOSPHODIESTERASE 4B2B



Characteristics **Release Date:** 26-Jul-2000 **Exp. Method:** X Ray Diffraction

Resolution: 1.77 Å

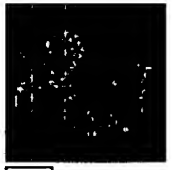
Classification **Hydrolase**

Compound **Mol. Id: 1 Molecule:** Phosphodiesterase 4b **Fragment:** Catalytic Domain **Mutation:** S487A, S489A

Authors **Xu, R.X., Hassell, A.M., Vanderwall, D., Lambert, M.H., Holmes, W.D., Luther, M.A., Rocque W.J., Milburn, M.V., Zhao, Y., Ke, H., Nolte, R.T.**

☑ **1OYN**

Crystal structure of PDE4D2 in complex with (R,S)-rolipram



Characteristics **Release Date:** 15-Jul-2003 **Exp. Method:** X Ray Diffraction

Resolution: 2.00 Å

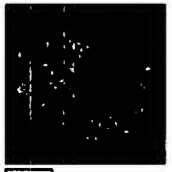
Classification **Hydrolase**

Compound **Mol. Id: 1 Molecule:** Camp Specific Phosphodiesterase Pde4d2 **Fragment:** Catalytic Domain

Authors **Huai, Q., Wang, H., Sun, Y., Kim, H.Y., Liu, Y., Ke, H.**

☑ **1Q9M**

Three dimensional structures of PDE4D in complex with roliprams and implication on inhibitor selectivity



Characteristics **Release Date:** 02-Sep-2003 **Exp. Method:** X Ray Diffraction

Resolution: 2.30 Å

Classification **Hydrolase**

Compound **Mol. Id: 1 Molecule:** Camp Specific Phosphodiesterase Pde4d2

Authors **Huai, Q., Wang, H., Sun, Y., Kim, H.Y., Liu, Y., Ke, H.**

1 2 3 4 5

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Thursday, June 22, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L4	L3 and crystal	26
☐	L3	phosphodiesterase 1B or PDE1B or PDE 1b	85
	DB=USPT,USOC,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L2	L1 and crystal	9
☐	L1	phosphodiesterase 1B or PDE1B or PDE 1b	54

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 9 of 9 returned.

☐ 1. Document ID: US 7034027 B2

L2: Entry 1 of 9 File: USPT Apr 25, 2006

US-PAT-NO: 7034027
DOCUMENT-IDENTIFIER: US 7034027 B2

TITLE: Fused heterocyclic derivatives as phosphodiesterase inhibitors

DATE-ISSUED: April 25, 2006

PRIOR-PUBLICATION:

DOC-ID	DATE
US 20030207867 A1	November 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Orme; Mark W.	Seattle	WA		US
Sawyer; Jason Scott	Indianapolis	IN		US
Schultze; Lisa M.	Woodinville	WA		US

US-CL-CURRENT: 514/250; 544/343

ABSTRACT:

Compounds of general structural formula (I) and use of the compounds and salts and solvates thereof, as therapeutic agents.

21 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: US 7022856 B2

L2: Entry 2 of 9 File: USPT Apr 4, 2006

US-PAT-NO: 7022856
DOCUMENT-IDENTIFIER: US 7022856 B2

TITLE: Carboline derivatives

DATE-ISSUED: April 4, 2006

PRIOR-PUBLICATION:

DOC-ID	DATE
US 20040122035 A1	June 24, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Orme; Mark W.	Seattle	WA		US
Sawyer; Jason S.	Indianapolis	IN		US
Bombrun; Agnes	Monnetier			FR
Gosmini; Romain L.	Les Ulis			FR
Bouillot; Anne	Les Ulis			FR
Dodic; Nerina	Les Ulis			FR
Sierra; Michael	Les Ulis			FR

US-CL-CURRENT: 546/85; 544/122, 544/277, 544/284, 544/331, 544/333, 546/86, 546/87

ABSTRACT:

Compounds of the general structural formula ##STR00001## and use of the compounds and salts and solvates thereof, as therapeutic agents.

18 Claims, 0 Drawing figures
Exemplary Claim Number: 1

☐ 3. Document ID: US 6872721 B2

L2: Entry 3 of 9 File: USPT Mar 29, 2005

US-PAT-NO: 6872721
DOCUMENT-IDENTIFIER: US 6872721 B2
**** See image for Certificate of Correction ****

TITLE: Derivatives of 2,3,6,7,12,12a-hexahydropyrazino-[1',2':1,6]pyrido[3,4b]-indole-1,4-dione

DATE-ISSUED: March 29, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Orme; Mark W.	Seattle	WA		
Sawyer; Jason Scott	Indianapolis	IN		
Daugan; Alain Claude-Marie	Les Ulis			FR

US-CL-CURRENT: 514/250; 544/342, 544/343

ABSTRACT:

Compounds of the general structural formula (I) and use of the compounds and salts and solvates thereof, as therapeutic agents. ##STR1##

21 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 4. Document ID: US 6858600 B2

L2: Entry 4 of 9 File: USPT Feb 22, 2005

US-PAT-NO: 6858600
DOCUMENT-IDENTIFIER: US 6858600 B2
** See image for Certificate of Correction **

TITLE: Proteomimetic compounds and methods

DATE-ISSUED: February 22, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hamilton; Andrew D.	Guilford	CT		
Ernst; Justin	New Heaven	CT		
Orner; Brendan P.	Madison	WI		

US-CL-CURRENT: 514/183; 514/252.12, 544/336, 544/358, 544/392

ABSTRACT:

The present invention relates to compounds and pharmaceutical compositions which are proteomimetic and to methods for inhibiting the interaction of an alpha-helical protein with another protein or binding site. Methods for treating diseases or conditions which are modulated through interactions between alpha helical proteins and their binding sites are other aspects of the invention.

48 Claims, 20 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 5. Document ID: US 6740655 B2

L2: Entry 5 of 9 File: USPT May 25, 2004

US-PAT-NO: 6740655
DOCUMENT-IDENTIFIER: US 6740655 B2

TITLE: Pyrimidine carboxamides useful as inhibitors of PDE4 isozymes

DATE-ISSUED: May 25, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Magee; Thomas Victor	Mystic	CT		
Marfat; Anthony	Mystic	CT		
Chambers; Robert James	Mystic	CT		

US-CL-CURRENT: 514/255.05; 514/269, 544/319

ABSTRACT:

This invention is directed to compounds of the formula: ##STR1##

wherein j is 0 or 1; k is 0 or 1; m is 0 or 1; n is 0 or 1; W is --O--; --S(.dbd.O).sub.t --, where t is 0, 1, or 2; or --N(R.sup.3)--; where R.sup.3 is --H, --(C.sub.1 -C.sub.3) alkyl, --OR.sup.12, phenyl, or benzyl; R.sup.C and R.sup.D have the same meaning as R.sup.A and R.sup.B, except that at least one of R.sup.C and R.sup.D must be --H; and the other variables are defined as set forth in the specification. The invention is also directed to pharmaceutical compositions comprising the above compounds and to methods of treating a subject suffering from a disease, disorder or condition mediated by the PDE4 isozyme, the method comprising administering a therapeutically effective amount of a compound as described above. The invention is particularly directed to methods of treating inflammatory, respiratory and allergic diseases and conditions, especially asthma; chronic obstructive pulmonary disease (COPD) including chronic bronchitis, emphysema, and bronchiectasis; chronic rhinitis; and chronic sinusitis.

15 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 6. Document ID: US 6569890 B2

L2: Entry 6 of 9 File: USPT May 27, 2003

US-PAT-NO: 6569890
DOCUMENT-IDENTIFIER: US 6569890 B2
**** See image for Certificate of Correction ****

TITLE: Cyclic AMP-specific phosphodiesterase inhibitors

DATE-ISSUED: May 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Martins; Timothy J.	Bothell	WA		
Fowler; Kerry W.	Seattle	WA		
Oliver; Amy	Bothell	WA		

Hertel; Carmen C.	Snohomish	WA

US-CL-CURRENT: 514/423; 548/531

ABSTRACT:

Pyrrole compounds that are potent and selective inhibitors of PDE4, as well as methods of making the same, are disclosed. Use of the compounds in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, also is disclosed.

28 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 7. Document ID: US 6372777 B1

L2: Entry 7 of 9 File: USPT Apr 16, 2002

US-PAT-NO: 6372777
DOCUMENT-IDENTIFIER: US 6372777 B1
**** See image for Certificate of Correction ****

TITLE: Cyclic AMP-specific phosphodiesterase inhibitors

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Martins; Timothy J.	Bothell	WA		
Fowler; Kerry W.	Seattle	WA		
Oliver; Amy	Bothell	WA		
Hertel; Carmen C.	Snohomish	WA		

US-CL-CURRENT: 514/423; 548/531

ABSTRACT:

Pyrrole compounds that are potent and selective inhibitors of PDE4, as well as methods of making the same, are disclosed. Use of the compounds in the treatment of inflammatory diseases and other diseases involving elevated levels of cytokines, as well as central nervous system (CNS) disorders, also is disclosed.

26 Claims, 1 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 8. Document ID: WO 2004087906 A1

L2: Entry 8 of 9 File: EPAB Oct 14, 2004

PUB-NO: WO2004087906A1
DOCUMENT-IDENTIFIER: WO 2004087906 A1
TITLE: CRYSTAL STRUCTURE OF 3',5'-CYCLIC NUCLEOTIDE PHOSPHODIESTERASE 1B (PDE1B) AND USES THEREOF

PUBN-DATE: October 14, 2004

INVENTOR-INFORMATION:

NAME	COUNTRY
PANDIT, JAYVARDHAN	US

INT-CL (IPC): C12 N 9/16; A61 K 31/00; G01 N 33/68
EUR-CL (EPC): C12N009/16

ABSTRACT:

CHG DATE=20041026 STATUS=O>Crystal structures of phosphodiesterase 1B (PDE1B), and the 3-D atomic coordinates of the PDE1B binding domain, are described and used to obtain PDE1B ligands, including PDE1B inhibitors. The inhibitors are formulated into pharmaceutical compositions and used to treat various psychological disorders.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 9. Document ID: EP 1613747 A1, WO 2004087906 A1, US 20050075795 A1

L2: Entry 9 of 9 File: DWPI Jan 11, 2006

DERWENT-ACC-NO: 2004-737705
DERWENT-WEEK: 200604

TITLE: Mammalian phosphodiesterase 1B crystal, useful for designing, modifying and assessing the activity of potential inhibitors that are useful as psychotherapeutics

INVENTOR: PANDIT, J

PRIORITY-DATA: 2003US-458946P (March 31, 2003), 2004US-0815390 (March 31, 2004)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1613747 A1	January 11, 2006	E	000	C12N009/16
WO 2004087906 A1	October 14, 2004	E	110	C12N009/16
US 20050075795 A1	April 7, 2005		000	G06F019/00

INT-CL (IPC): A61 K 31/00; C12 N 9/16; G01 N 31/00; G01 N 33/48; G01 N 33/50; G01 N 33/68; G06 F 19/00

ABSTRACTED-PUB-NO: WO2004087906A
BASIC-ABSTRACT:

NOVELTY - A mammalian phosphodiesterase 1B (PDE1B) crystal (I), comprises a fully defined sequence of 536 amino acids (S1), as given in the specification, or its homologue or variant.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a crystal (II) of a PDE1B-PDE1B ligand complex, where the ligand is an antagonist or an inhibitor;

(2) a crystal complex (III) comprising a polypeptide with an amino acid sequence spanning amino acids Thr142 to Gln507 listed in (S1), its homologue or variant;

(3) a polypeptide (IV) comprising (S1) or its homologue or variant, where the molecules are arranged in a crystalline manner belonging to space group P43212 with unit cell dimensions a = 87.47 Angstrom , b = 87.47 Angstrom , c = 135.03 Angstrom , alpha = beta = gamma = 90.0 deg. , and which effectively diffracts X-rays for determination of the atomic coordinates of PDE1B polypeptide to a resolution of about 1.8 Angstrom ;

(4) a computer (V):

(a) for producing a three-dimensional representation of a polypeptide with an amino acid sequence spanning amino acids Thr142-Gln507 listed in (S1), or its homologue, or variant,

(b) for producing a three-dimensional representation of molecule or molecular complex comprising (C1),

(c) for producing three-dimensional representation of molecule or molecular complex comprising the atomic coordinates having a root mean square deviation of less than +/-2.0, 1.7, 1.5, 1.2, 1.0, 0.7, 0.5 or even 0.2 Angstrom from the atomic coordinates for the carbon back bone atoms listed in (C1), or

(d) for producing three-dimensional representation of molecule or molecular complex comprising a binding site defined by (C1), or a structural coordinates of portion of the residues in (C1), or the structural coordinates of one or more PDE1B amino acids in (S1) chosen from His223, His373, Thr385, Leu388, Ser420, Gln421, and Phe424, where (V) comprises a computer readable data storage medium comprising a data storage material encoded with computer-readable data, where the data comprises the structure coordinates (C1) of PDE1B C-terminal catalytic domain crystal, as given in the specification or its portions, a working memory for storing instructions for processing the computer readable data, a central processing unit coupled to the working memory and to the computer-readable data storage medium for processing the computer-machine readable data into three-dimensional representation, and a display coupled to the central processing unit for displaying the representation;

(5) identifying a potential ligands for PDE1B, or its homologues, analogues or variants, by displaying three-dimensional structures of PDE1B enzymes, or its portions, as defined by (C1), on a computer display screen, optionally replacing one or more PDE1B amino acid residues listed in (S1), or one or more of the amino acids that are near the binding pocket in PDE1B catalytic domain at a distance of 10 Angstrom , 7 Angstrom or 4 Angstrom away from the ligand of PDE1B, or one or more amino acid residues chosen from His223, His373, Thr385, Leu388, Ser420,

Gln421, and Phe424, in the three-dimensional structure with a different naturally occurring amino acid or an unnatural amino acid, employing the three-dimensional structure to design or select the ligand, contacting the ligand with PDE1B, or its variant, in the presence of one or more substrates, measuring the ability of the ligand to modulate the activity of PED1B, computationally modifying the structure of the ligand, and computationally determining the fit of the modified ligand with the three-dimensional coordinates of PDE1B, or its portions;

(6) treating psychological disorders comprising administering to a patient in need of treatment the pharmaceutical compositions of ligands identified by structure-based drug design using the atomic coordinates substantially similar to or portions of (C1), where the psychological disorder is chosen from multiple variants of schizophrenia, anxiety disorders, movement disorders chosen from Huntington's disease, Parkinson's disease and dyskinesia, alcohol and drug addictions, cognitive deficiencies, and mood disorders; and

(7) an expression vector useful in method for preparing a purified catalytic domain of PDE1B comprising a polypeptide with an amino acid sequence spanning amino acids Thr142 to Gln507 listed in (S1) or its homologue or variant.

USE - (I) is useful for designing, modifying and assessing the activity of potential inhibitors of the enzyme, that are useful as psychotherapeutics.

DESCRIPTION OF DRAWING(S) - The figure shows an orthogonal view of the structure of phosphodiesterase 1B (PDE1B) in ribbon representation.

Hit List

First Hit | Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Search Results - Record(s) 1 through 26 of 26 returned.

☐ 1. Document ID: US 20060110783 A1

L4: Entry 1 of 26 File: PGPB May 25, 2006

PGPUB-DOCUMENT-NUMBER: 20060110783
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060110783 A1

TITLE: Diagnostics and therapeutics for diseases associated with human phosphodiesterase 10a (pde10a)

PUBLICATION-DATE: May 25, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Golz; Stefan	Essen		DE
Bruggemeier; Ulf	Leichlingen		DE
Geerts; Andreas	Wuppertal		DE

US-CL-CURRENT: 435/21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 2. Document ID: US 20060100218 A1

L4: Entry 2 of 26 File: PGPB May 11, 2006

PGPUB-DOCUMENT-NUMBER: 20060100218
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060100218 A1

TITLE: PDE4B inhibitors

PUBLICATION-DATE: May 11, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Ibrahim; Prabha N.	Mountain View	CA	US
Bremer; Ryan	Albany	CA	US
Gillette; Sam	Oakland	CA	US
Cho; Hanna	Oakland	CA	US
Nespi; Marika	Berkeley	CA	US

Mamo; Shumeye	Oakland	CA	US
Zhang; Chao	Moraga	CA	US
Artis; Dean R.	Kensington	CA	US
Lee; Byunghun	Marina	CA	US
Zuckerman; Rebecca	Alameda	CA	US

US-CL-CURRENT: 514/256; 514/314, 514/338, 514/375, 514/406, 544/330, 546/113, 546/271.7, 546/277.4, 548/216, 548/361.1, 548/465, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 3. Document ID: US 20060051370 A1

L4: Entry 3 of 26 File: PGPB Mar 9, 2006

PGPUB-DOCUMENT-NUMBER: 20060051370
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060051370 A1

TITLE: Microorganisms for therapy

PUBLICATION-DATE: March 9, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Szalay; Aladar A.	Highland	CA	US
Timiryasova; Tatyana	Scotrun	PA	US
Yu; Yong A.	San Diego	CA	US
Zhang; Qian	San Diego	CA	US

US-CL-CURRENT: 424/199.1; 514/44

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 4. Document ID: US 20060041006 A1

L4: Entry 4 of 26 File: PGPB Feb 23, 2006

PGPUB-DOCUMENT-NUMBER: 20060041006
PGPUB-FILING-TYPE:
DOCUMENT-IDENTIFIER: US 20060041006 A1

TITLE: PDE4B inhibitors and uses therefor

PUBLICATION-DATE: February 23, 2006

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Ibrahim; Prabha N.	Mountain View	CA	US
Cho; Hanna	Oakland	CA	US

England; Bruce	Hayward	CA	US
Gillette; Sam	Oakland	CA	US
Artis; Dean R.	Kensington	CA	US
Zuckerman; Rebecca	Alameda	CA	US
Zhang; Chao	Moraga	CA	US

US-CL-CURRENT: 514/422; 514/423, 514/447, 514/471, 548/517, 548/530, 549/480, 549/59, 549/63

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 5. Document ID: US 20050215563 A1

L4: Entry 5 of 26 File: PGPB Sep 29, 2005

PGPUB-DOCUMENT-NUMBER: 20050215563
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050215563 A1

TITLE: Proteomimetic compounds and methods

PUBLICATION-DATE: September 29, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Hamilton, Andrew D.	Guilford	CT	US
Ernst, Justin	San Diego	CA	US
Orner, Brendan P.	Madison	WI	US

US-CL-CURRENT: 514/252.17; 514/253.01, 514/266.21, 514/266.22, 544/284, 544/360

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 6. Document ID: US 20050202550 A1

L4: Entry 6 of 26 File: PGPB Sep 15, 2005

PGPUB-DOCUMENT-NUMBER: 20050202550
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050202550 A1

TITLE: Crystal structure of 3', 5'-cyclic nucleotide phosphodiesterase (PDE10A) and uses thereof

PUBLICATION-DATE: September 15, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Pandit, Jayvardhan	Mystic	CT	US

US-CL-CURRENT: 435/196; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 7. Document ID: US 20050101581 A1

L4: Entry 7 of 26 File: PGPB May 12, 2005

PGPUB-DOCUMENT-NUMBER: 20050101581
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050101581 A1

TITLE: Therapeutic treatment methods 2

PUBLICATION-DATE: May 12, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Reading, Christopher L.	San Diego	CA	US
Ahlem, Clarence N.	San Diego	CA	US
Auci, Dominick L.	San Diego	CA	US
Dowding, Charles	San Diego	CA	US
Frincke, James M.	San Diego	CA	US
Li, Mei	San Diego	CA	US
Page, Theodore M.	Carlsbad	CA	US
Stickney, Dwight R.	Granite Bay	CA	US
Trauger, Richard J.	Leucadia	CA	US
White, Steven K.	San Diego	CA	US

US-CL-CURRENT: 514/178

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 8. Document ID: US 20050079548 A1

L4: Entry 8 of 26 File: PGPB Apr 14, 2005

PGPUB-DOCUMENT-NUMBER: 20050079548
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050079548 A1

TITLE: Ligand development using PDE4B crystal structures

PUBLICATION-DATE: April 14, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Artis, Dean R.	Kensington	CA	US
Bollag, Gideon	Hercules	CA	US

Card, Graeme	Oakland	CA	US
Martin, Fernando	Toronto	CA	CA
Milburn, Michael V.	Emeryville	CA	US
Zhang, Kam	Walnut Creek		US

US-CL-CURRENT: 435/7.1; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 9. Document ID: US 20050075795 A1

L4: Entry 9 of 26 File: PGPB Apr 7, 2005

PGPUB-DOCUMENT-NUMBER: 20050075795
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050075795 A1

TITLE: Crystal structure of 3', 5'-cyclic nucleotide phosphodiesterase (PDE1B) and uses thereof

PUBLICATION-DATE: April 7, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Pandit, Jayvardhan	Mystic	CT	US

US-CL-CURRENT: 702/20

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 10. Document ID: US 20050048573 A1

L4: Entry 10 of 26 File: PGPB Mar 3, 2005

PGPUB-DOCUMENT-NUMBER: 20050048573
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050048573 A1

TITLE: PDE5A crystal structure and uses

PUBLICATION-DATE: March 3, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Artis, Dean R.	Kensington	CA	US
Bollag, Gideon	Orinda	CA	US
Card, Graeme	Oakland	CA	US
Martin, Fernando	Toronto	NC	CA
Milburn, Michael V.	Cary	CA	US
Zhang, Kam	Walnut Creek		US

US-CL-CURRENT: 435/7.1; 436/518

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 11. Document ID: US 20050031643 A1

L4: Entry 11 of 26 File: PGPB Feb 10, 2005

PGPUB-DOCUMENT-NUMBER: 20050031643
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20050031643 A1

TITLE: Microorganisms for therapy

PUBLICATION-DATE: February 10, 2005

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Szalay, Aladar A.	Highland	CA	US
Timiryasova, Tatyana	San Diego	CA	US
Yu, Yong A.	San Diego	CA	US
Zhang, Qian	San Diego	CA	US

US-CL-CURRENT: 424/199.1; 435/235.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 12. Document ID: US 20040197914 A1

L4: Entry 12 of 26 File: PGPB Oct 7, 2004

PGPUB-DOCUMENT-NUMBER: 20040197914
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040197914 A1

TITLE: Viral delivery systems and related manufacture and use

PUBLICATION-DATE: October 7, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Wasilko, David J.	Oakdale	CT	US
Lee, S. Edward	Waterford	CT	US
Hermans, William R.	Millbury	MA	US

US-CL-CURRENT: 435/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 13. Document ID: US 20040171798 A1

L4: Entry 13 of 26 File: PGPB Sep 2, 2004

PGPUB-DOCUMENT-NUMBER: 20040171798
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040171798 A1

TITLE: Nicotinamide acids, amides, and their mimetics active as inhibitors of PDE4 isozymes

PUBLICATION-DATE: September 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Magee, Thomas V.	Mystic	CT	US
Marfat, Anthony	Mystic	CT	US
Chambers, Robert J.	Mystic	CT	US

US-CL-CURRENT: 530/331; 546/315

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 14. Document ID: US 20040138187 A1

L4: Entry 14 of 26 File: PGPB Jul 15, 2004

PGPUB-DOCUMENT-NUMBER: 20040138187
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040138187 A1

TITLE: Therapeutic treatment methods

PUBLICATION-DATE: July 15, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Reading, Christopher L.	San Diego	CA	US
Ahlem, Clarence N.	San Diego	CA	US
Auci, Dominick L.	San Diego	CA	US
Dowding, Charles	San Diego	CA	US
Frincke, James M.	San Diego	CA	US
Li, Mei	San Diego	CA	US
Page, Theodore M.	Carlsbad	CA	US
Stickney, Dwight R.	Granite Bay	CA	US
Trauger, Richard J.	Leucadia	CA	US
White, Steven K.	San Diego	CA	US

US-CL-CURRENT: 514/169

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 15. Document ID: US 20040122035 A1

L4: Entry 15 of 26 File: PGPB Jun 24, 2004

PGPUB-DOCUMENT-NUMBER: 20040122035
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040122035 A1

TITLE: Chemical compounds

PUBLICATION-DATE: June 24, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Orme, Mark W.	Seattle	WA	US
Sawyer, Jason S	Indianapolis	IN	US
Bombrun, Agnes	Monnetier		FR
Gosmini, Romain L	Les Ulis		FR
Bouillot, Anne	Les Ulis		FR
Dodic, Nerina	Les Ulis		FR
Sierra, Michael	Les Ulis		FR

US-CL-CURRENT: 514/291; 546/85

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 16. Document ID: US 20030225092 A1

L4: Entry 16 of 26 File: PGPB Dec 4, 2003

PGPUB-DOCUMENT-NUMBER: 20030225092
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030225092 A1

TITLE: Chemical compounds

PUBLICATION-DATE: December 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Orme, Mark W.	Seattle	WA	US
Sawyer, Jason Scott	Indianapolis	IN	US
Daugan, Alain Claude-Marie	Les Ulis		FR

US-CL-CURRENT: 514/249; 544/343

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 17. Document ID: US 20030207867 A1

L4: Entry 17 of 26 File: PGPB Nov 6, 2003

PGPUB-DOCUMENT-NUMBER: 20030207867
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030207867 A1

TITLE: Fused heterocyclic derivatives as phosphodiesterase inhibitors

PUBLICATION-DATE: November 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Orme, Mark W.	Seattle	WA	US
Sawyer, Jason Scott	Indianapolis	IN	US
Schultze, Lisa M	Woodinville	WA	US

US-CL-CURRENT: 514/222.8; 514/217.05, 514/229.2, 514/243, 514/249, 544/183, 544/343, 544/66, 544/9

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 18. Document ID: US 20030186989 A1

L4: Entry 18 of 26 File: PGPB Oct 2, 2003

PGPUB-DOCUMENT-NUMBER: 20030186989
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030186989 A1

TITLE: Nicotinamide benzofused-heterocyclyl derivatives useful as selective inhibitors of pde4 isozymes

PUBLICATION-DATE: October 2, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Marfat, Anthony	Mystic	CT	US
Chambers, Robert James	Mystic	CT	US

US-CL-CURRENT: 514/252.02; 514/255.05, 514/256, 514/269, 514/332, 514/340, 514/341, 514/342, 544/238, 544/295, 544/296, 544/405, 546/261, 546/262, 546/268.1, 546/268.7, 546/269.1, 546/269.7, 546/271.4, 546/272.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 19. Document ID: US 20030144300 A1

L4: Entry 19 of 26 File: PGPB Jul 31, 2003

PGPUB-DOCUMENT-NUMBER: 20030144300
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030144300 A1

TITLE: Pyrimidine carboxamides useful as inhibitors of pde4 isozymes

PUBLICATION-DATE: July 31, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Magee, Thomas Victor	Mystic	CT	US
Marfat, Anthony	Mystic	CT	US
Chambers, Robert James	Mystic	CT	US

US-CL-CURRENT: 514/256; 514/269, 544/314, 544/326, 544/328

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 20. Document ID: US 20030068831 A1

L4: Entry 20 of 26 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068831
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068831 A1

TITLE: Proteins and druggable regions of proteins

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Edwards, Aled	Toronto	CA	CA
Arrowsmith, Cheryl	North York		CA
Greenblatt, Jack	Toronto		CA
Mendlein, John D.	Encincitas		US

US-CL-CURRENT: 436/518; 435/7.1, 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 21. Document ID: US 20030068651 A1

L4: Entry 21 of 26 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068651
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068651 A1

TITLE: Multi-target analysis of gene families for chemistry of high affinity and selective small molecules and other therapeutics

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Arrowsmith, Cheryl	North York	CA	CA
Greenblatt, Jack	Toronto		CA
Edwards, Aled	Toronto		CA
Mendlein, John D.	Encincitas		US

US-CL-CURRENT: 435/7.1; 702/19

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 22. Document ID: US 20030068650 A1

L4: Entry 22 of 26 File: PGPB Apr 10, 2003

PGPUB-DOCUMENT-NUMBER: 20030068650
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030068650 A1

TITLE: Target analysis for chemistry of specific and broad spectrum anti-infectives and other therapeutics

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Greenblatt, Jack	Toronto	CA	CA
Edwards, Aled	Toronto		CA
Arrowsmith, Cheryl	North York		CA
Mendlein, John D.	Encincitas		US

US-CL-CURRENT: 435/7.1; 435/5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 23. Document ID: US 20030031681 A1

L4: Entry 23 of 26 File: PGPB Feb 13, 2003

PGPUB-DOCUMENT-NUMBER: 20030031681
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030031681 A1

TITLE: Combined growth factor-deleted and thymidine kinase-deleted vaccinia virus vector

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
McCart, J. Andrea	Toronto	PA	CA
Bartlett, David L.	Pittsburgh	MD	US
Moss, Bernard	Bethesda		US

US-CL-CURRENT: 424/186.1; 435/235.1, 435/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 24. Document ID: US 20030013754 A1

L4: Entry 24 of 26 File: PGPB Jan 16, 2003

PGPUB-DOCUMENT-NUMBER: 20030013754
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030013754 A1

TITLE: Cyclic AMP-specific phosphodiesterase inhibitors

PUBLICATION-DATE: January 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Martins, Timothy J.	Bothell	WA	US
Fowler, Kerry W.	Seattle	WA	US
Oliver, Amy	Bothell	WA	US
Hertel, Carmen C.	Snohomish	WA	US

US-CL-CURRENT: 514/422; 514/423, 548/517, 548/530

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. D

☐ 25. Document ID: US 20030008882 A1

L4: Entry 25 of 26 File: PGPB Jan 9, 2003

PGPUB-DOCUMENT-NUMBER: 20030008882
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030008882 A1

TITLE: Proteomimetic compounds and methods

PUBLICATION-DATE: January 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Hamilton, Andrew D.	Guilford	CT	US

Ernst, Justin	San Diego	CA	US
Orner, Brendan P.	Madison	WI	US

US-CL-CURRENT: 514/255.03; 514/255.02, 514/256, 514/277, 514/317, 514/365, 514/374, 514/396, 514/408, 514/461, 514/571, 544/335, 544/385, 544/392, 546/216, 546/341, 548/202, 548/215, 548/354.1, 548/577, 562/466

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 26. Document ID: US 20020111495 A1

L4: Entry 26 of 26 File: PGPB Aug 15, 2002

PGPUB-DOCUMENT-NUMBER: 20020111495
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020111495 A1

TITLE: Nicotinamide acids, amides, and their mimetics active as inhibitors of PDE4 isozymes

PUBLICATION-DATE: August 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY
Magee, Thomas Victor	Mystic	CT	US
Marfat, Anthony	Mystic	CT	US
Chambers, Robert James	Mystic	CT	US

US-CL-CURRENT: 546/291; 546/298, 546/315

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

Clear | Generate Collection | Print | Fwd Refs | Bkwd Refs | Generate OACS

Terms	Documents
L3 and crystal	26

Display Format: CIT Change Format

Previous Page Next Page Go to Doc#

FILE 'HOME' ENTERED AT 11:06:41 ON 22 JUN 2006

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=> file .nash
=> s (cyclic nucleotide phosphodiesterase or PDE1B) and (crystal or X-ray)
L1           58 FILE MEDLINE
L2           52 FILE CAPLUS
L3           60 FILE SCISEARCH
L4           12 FILE LIFESCI
L5           21 FILE BIOSIS
L6           23 FILE EMBASE

TOTAL FOR ALL FILES
L7          226 (CYCLIC NUCLEOTIDE PHOSPHODIESTERASE OR PDE1B) AND (CRYSTAL OR
                X-RAY)

=> s l7 not 2004-2006/py
L8           38 FILE MEDLINE
L9           27 FILE CAPLUS
L10          32 FILE SCISEARCH
L11           8 FILE LIFESCI
L12          14 FILE BIOSIS
L13          14 FILE EMBASE

TOTAL FOR ALL FILES
L14         133 L7 NOT 2004-2006/PY

=> s l14 and catalytic domain
L15           8 FILE MEDLINE
L16           4 FILE CAPLUS
L17           7 FILE SCISEARCH
L18           1 FILE LIFESCI
L19           6 FILE BIOSIS
L20           4 FILE EMBASE

TOTAL FOR ALL FILES
L21          30 L14 AND CATALYTIC DOMAIN

=> dup rem l21
PROCESSING COMPLETED FOR L21
L22          13 DUP REM L21 (17 DUPLICATES REMOVED)

=> d ibib abs 1-13

L22  ANSWER 1 OF 13     MEDLINE on STN                  DUPLICATE 1
ACCESSION NUMBER:   2003573643     MEDLINE Full-text
DOCUMENT NUMBER:    PubMed ID: 14609333
TITLE:              The crystal structure of AMP-bound PDE4 suggests
                    a mechanism for phosphodiesterase catalysis.
AUTHOR:             Huai Qing; Colicelli John; Ke Hengming
CORPORATE SOURCE:   Department of Biochemistry and Biophysics and Lineberger
                    Comprehensive Cancer Center, The University of North
                    Carolina, Chapel Hill, North Carolina 27599-7260, USA.
CONTRACT NUMBER:    GM59791 (NIGMS)
                    NS31911 (NINDS)
SOURCE:             Biochemistry, (2003 Nov 18) Vol. 42, No. 45, pp. 13220-6.
                    Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
OTHER SOURCE:       PDB-1PTW
ENTRY MONTH:        200403
ENTRY DATE:         Entered STN: 16 Dec 2003
                    Last Updated on STN: 5 Mar 2004
                    Entered Medline: 4 Mar 2004
AB     Cyclic nucleotide phosphodiesterases (PDEs) regulate the intracellular concentrations of
       cyclic 3',5'-adenosine and guanosine monophosphates (cAMP and cGMP, respectively) by
       hydrolyzing them to AMP and GMP, respectively.  Family-selective inhibitors of PDEs have
```

been studied for treatment of various human diseases. However, the catalytic mechanism of cyclic nucleotide hydrolysis by PDEs has remained unclear. We determined the crystal structure of the human PDE4D2 catalytic domain in complex with AMP at 2.4 A resolution. In this structure, two divalent metal ions simultaneously interact with the phosphate group of AMP, implying a binuclear catalysis. In addition, the structure suggested that a hydroxide ion or a water bridging two metal ions may serve as the nucleophile for the hydrolysis of the cAMP phosphodiester bond.

L22 ANSWER 2 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2003346036 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12878217
TITLE: The role of tryptophan 1072 in human PDE3B inhibitor binding.
AUTHOR: Chung Christine; Varnerin Jeffrey P; Morin Nancy R; MacNeil Douglas J; Singh Suresh B; Patel Sangita; Scapin Giovanna; Van der Ploeg Lex H T; Tota Michael R
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, P.O. Box 2000, Mailstop: RY80M-213, Rahway, NJ 07065, USA.
SOURCE: Biochemical and biophysical research communications, (2003 Aug 8) Vol. 307, No. 4, pp. 1045-50.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 25 Jul 2003
Last Updated on STN: 13 Sep 2003
Entered Medline: 12 Sep 2003

AB The catalytic domain of recombinant human PDE3B was expressed in Escherichia coli as inclusion bodies and refolded to form active enzyme. A mutation at tryptophan 1072 in PDE3B disrupts inhibitor binding, but has minimal effect on cAMP hydrolysis. The W1072A mutation caused a 158-fold decrease in affinity for cilostamide, a 740-fold decrease for cGMP, and a 15-fold decrease in affinity for IBMX. The corresponding tyrosine mutation had a smaller effect. However, the K(m) of cAMP for the W1072A mutation was only increased by about 7-fold. The data indicate that the inhibitor binding region is not completely coincident with the substrate binding region. The homologous residue in PDE4B is located on helix 16 within 7A of the predicted bound substrate. A model of PDE3B was constructed based on the X-ray crystal structure of PDE4B.

L22 ANSWER 3 OF 13 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003315344 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12842049
TITLE: Three-dimensional structures of PDE4D in complex with roliprams and implication on inhibitor selectivity.
AUTHOR: Huai Qing; Wang Huanchen; Sun Yingjie; Kim Hwa-Young; Liu Yudong; Ke Hengming
CORPORATE SOURCE: Department of Biochemistry and Biophysics and Lineberger Comprehensive Cancer Center, The University of North Carolina, Chapel Hill, Chapel Hill, NC 27599, USA.
CONTRACT NUMBER: GM59791 (NIGMS)
SOURCE: Structure (Cambridge, Mass. : 2001), (2003 Jul) Vol. 11, No. 7, pp. 865-73.
Journal code: 101087697. ISSN: 0969-2126.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1OYM; PDB-1OYN
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 8 Jul 2003
Last Updated on STN: 20 Mar 2004
Entered Medline: 19 Mar 2004

AB Selective inhibitors against the 11 families of cyclic nucleotide phosphodiesterases (PDEs) are used to treat various human diseases. How the inhibitors selectively bind the conserved PDE catalytic domains is unknown. The crystal structures of the PDE4D2 catalytic domain in complex with (R)- or (R,S)-rolipram suggest that inhibitor selectivity is determined by the chemical nature of amino acids and subtle conformational changes of

the binding pockets. The conformational states of Gln369 in PDE4D2 may play a key role in inhibitor recognition. The corresponding Y329S mutation in PDE7 may lead to loss of the hydrogen bonds between rolipram and Gln369 and is thus a possible reason explaining PDE7's insensitivity to rolipram inhibition. Docking of the PDE5 inhibitor sildenafil into the PDE4 catalytic pocket further helps understand inhibitor selectivity.

L22 ANSWER 4 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:712953 SCISEARCH Full-text
THE GENUINE ARTICLE: 583YG
TITLE: Identification of interaction sites of cyclic nucleotide phosphodiesterase type 3A with milrinone and cilostazol using molecular modeling and site-directed mutagenesis
AUTHOR: Zhang W; Ke H; Colman R W (Reprint)
CORPORATE SOURCE: Temple Univ, Sch Med, Sol Sherry Thrombosis Res Ctr, 3400 N Broad St, Philadelphia, PA 19140 USA (Reprint); Temple Univ, Sch Med, Sol Sherry Thrombosis Res Ctr, Philadelphia, PA 19140 USA; Univ N Carolina, Dept Biochem & Biophys, Chapel Hill, NC USA; Univ N Carolina, Lineberger Comprehens Canc Ctr, Chapel Hill, NC 27599 USA
COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR PHARMACOLOGY, (SEP 2002) Vol. 62, No. 3, pp. 514-520.
ISSN: 0026-895X.
PUBLISHER: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 22
ENTRY DATE: Entered STN: 13 Sep 2002
Last Updated on STN: 13 Sep 2002
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To identify amino acid residues involved in PDE3-selective inhibitor binding, we selected eight presumed interacting residues in the substrate-binding pocket of PDE3A using a model created on basis of homology to the PDE4B crystal structure. We changed the residues to alanine using site-directed mutagenesis technique, expressed the mutants in a baculovirus/ Sf9 cell system, and analyzed the kinetic characteristics of inhibition of the mutant enzymes by milrinone and cilostazol, specific inhibitors of PDE3. The mutants displayed differential sensitivity to the inhibitors. Mutants Y751A, D950A, and F1004A had reduced sensitivity to milrinone (K-i changed from 0.66 muM for the recombinant PDE3A to 7.5 to 156 muM for the mutants), and diminished sensitivity to cilostazol (K-i of the mutants were 18- to 371-fold higher than that of the recombinant PDE3A). In contrast, the mutants T844A, F972A and Q975A showed increased K-i for cilostazol but no difference for milrinone from the recombinant PDE3A. Molecular models show that the PDE3 inhibitors cilostazol and milrinone share some of common residues but interact with distinct residues at the active site, suggesting that selective inhibitors can be designed with flexible size against PDE3 active site. Our study implies that highly conserved residuals Y751, D950 and F1004 in the PDE families are key residues for binding of both substrate and inhibitors, and nonconserved T844 may be responsible for the cilostazol selectivity of PDE3A. Detailed knowledge of the structure of inhibitory sites should contribute to development of more potent and specific inhibitory drugs.

L22 ANSWER 5 OF 13 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002630336 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12387865
TITLE: Crystal structure of phosphodiesterase 4D and inhibitor complex(1).
AUTHOR: Lee Mi Eun; Markowitz Joseph; Lee Jie Oh; Lee Hayyoung
CORPORATE SOURCE: Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1 Kusong-dong, Yusong-gu, Daejon 305-701, South Korea.
SOURCE: FEBS letters, (2002 Oct 23) Vol. 530, No. 1-3, pp. 53-8.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 22 Oct 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 10 Dec 2002

AB Cyclic nucleotide phosphodiesterases (PDEs) regulate physiological processes by degrading intracellular second messengers, adenosine-3',5'-cyclic phosphate or guanosine-3',5'-cyclic phosphate. The first crystal structure of PDE4D catalytic domain and a bound inhibitor, zardaverine, was determined. Zardaverine binds to a highly conserved pocket that includes the catalytic metal binding site. Zardaverine fills only a portion of the active site pocket. More selective PDE4 inhibitors including rolipram, cilomilast and roflumilast have additional functional groups that can utilize the remaining empty space for increased binding energy and selectivity. In the crystal structure, the catalytic domain of PDE4D possesses an extensive dimerization interface containing residues that are highly conserved in PDE1, 3, 4, 8 and 9. Mutations of R358D or D322R among these interface residues prohibit dimerization of the PDE4D catalytic domain in solution.

L22 ANSWER 6 OF 13 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002026242 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11468344
TITLE: Identification of overlapping but distinct cAMP and cGMP interaction sites with cyclic nucleotide phosphodiesterase 3A by site-directed mutagenesis and molecular modeling based on crystalline PDE4B.
AUTHOR: Zhang W; Ke H; Tretiakova A P; Jameson B; Colman R W
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
CONTRACT NUMBER: P01 HL64943 (NHLBI)
RO1 GM59791 (NIGMS)
RO1 NS37726 (NINDS)
T32 HL07777 (NHLBI)
SOURCE: Protein science : a publication of the Protein Society, (2001 Aug) Vol. 10, No. 8, pp. 1481-9.
Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 21 Jan 2002
Last Updated on STN: 21 Jan 2002
Entered Medline: 7 Dec 2001

AB Cyclic nucleotide phosphodiesterase 3A (PDE3A) hydrolyzes cAMP to AMP, but is competitively inhibited by cGMP due to a low k(cat) despite a tight K(m). Cyclic AMP elevation is known to inhibit all pathways of platelet activation, and thus regulation of PDE3 activity is significant. Although cGMP elevation will inhibit platelet function, the major action of cGMP in platelets is to elevate cAMP by inhibiting PDE3A. To investigate the molecular details of how cGMP, a similar but not identical molecule to cAMP, behaves as an inhibitor of PDE3A, we constructed a molecular model of the catalytic domain of PDE3A based on homology to the recently determined X-ray crystal structure of PDE4B. Based on the excellent fit of this model structure, we mutated nine amino acids in the putative catalytic cleft of PDE3A to alanine using site-directed mutagenesis. Six of the nine mutants (Y751A, H840A, D950A, F972A, Q975A, and F1004A) significantly decreased catalytic efficiency, and had k(cat)/K(m) less than 10% of the wild-type PDE3A using cAMP as substrate. Mutants N845A, F972A, and F1004A showed a 3- to 12-fold increase of K(m) for cAMP. Four mutants (Y751A, H840A, D950A, and F1004A) had a 9- to 200-fold increase of K(i) for cGMP in comparison to the wild-type PDE3A. Studies of these mutants and our previous study identified two groups of amino acids: E866 and F1004 contribute commonly to both cAMP and cGMP interactions while N845, E971, and F972 residues are unique for cAMP and the residues Y751, H836, H840, and D950 interact with cGMP. Therefore, our results provide biochemical evidence that cGMP interacts with the active site residues differently from cAMP.

L22 ANSWER 7 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2002048827 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11776290
TITLE: CoMFA and CoMSIA 3D-quantitative structure-activity relationship model on benzodiazepine derivatives,

inhibitors of phosphodiesterase IV.
AUTHOR: Ducrot P; Andrianjara C R; Wrigglesworth R
CORPORATE SOURCE: Pfizer Global Research and Development, Fresnes Laboratories, France.. Pierre.ducrot@pfizer.com
SOURCE: Journal of computer-aided molecular design, (2001 Sep) Vol. 15, No. 9, pp. 767-85.
Journal code: 8710425. ISSN: 0920-654X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 11 Jun 2002
Entered Medline: 10 Jun 2002

AB Recently, we reported structurally novel PDE4 inhibitors based on 1,4-benzodiazepine derivatives. The main interest in developing bezodiazepine-based PDE4 inhibitors is in their lack of adverse effects of emesis with respect to rolipram-like compounds. A large effort has thus been made toward the structural optimization of this series. In the absence of structural information on the inhibitor binding mode into the PDE4 active site, 2D-QSAR (H-QSAR) and two 3D-QSAR (CoMFA and CoMSIA) methods were applied to improve our understanding of the molecular mechanism controlling the PDE4 affinity of the benzodiazepine derivatives. As expected, the CoMSIA 3D contour maps have provided more information on the benzodiazepine interaction mode with the PDE4 active site whereas CoMFA has built the best tool for activity prediction. The 2D pharmacophoric model derived from CoMSIA fields is consistent with the crystal structure of the PDE4 active site reported recently. The combination of the 2D and 3D-QSAR models was used not only to predict new compounds from the structural optimization process, but also to screen a large library of bezodiazepine derivatives.

L22 ANSWER 8 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:609133 SCISEARCH Full-text
THE GENUINE ARTICLE: 341MC
TITLE: Histidine-607 and histidine-643 provide important interactions for metal support of catalysis in phosphodiesterase-5
AUTHOR: Francis S H (Reprint); Turko I V; Grimes K A; Corbin J D
CORPORATE SOURCE: Vanderbilt Univ, Sch Med, Dept Mol Physiol & Biophys, Light Hall, Room 702, Nashville, TN 37232 USA (Reprint); Vanderbilt Univ, Sch Med, Dept Mol Physiol & Biophys, Nashville, TN 37232 USA
COUNTRY OF AUTHOR: USA
SOURCE: BIOCHEMISTRY, (8 AUG 2000) Vol. 39, No. 31, pp. 9591-9596.
ISSN: 0006-2960.
PUBLISHER: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 37
ENTRY DATE: Entered STN: 2000
Last Updated on STN: 2000
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Class I cyclic nucleotide phosphodiesterases (PDEs) share a catalytic domain containing 18 invariant residues. In cGMP-binding cCMP-specific PDE (PDE5), we showed previously that point mutation of nine of these profoundly decreases k(cat) when the assay is conducted in the presence of Mg2+; seven of these are in the prototypical metal-binding motifs A and B (HX3HXnE) that we identified earlier. Tandem arrangement of two of these metal-binding motifs in PDEs is novel, and whether residues within these motifs are involved in metal support of catalytic activity is a fundamental question in this field. This report shows that mutation of either His-607 (A motif) or His-643 (B motif) to alanine profoundly diminishes support of PDE catalysis by Mn2+ or Mg2+, but mutation of His-647 in B motif or of Glu in either motif does not. H607A and H643A mutants have much greater maximum catalytic rates supported by Mn2+ than that by Mg2+; catalytic activity of H603A mutant is supported weakly by either. In H607A and H643A, K(a)s for Mn2+ and Mg2+ are increased, but the effect of Mn2+ is 2-fold greater than that of Mg2+ in each. Mutation of any of the other conserved residues (Asn-604, Asp-644, His-675, Asp-714, and Asp-754) causes unremarkable changes in Mn2+ or Mg2+ support Of catalysis.

This study identifies specific residues in PDES that contribute to interactions with catalytically relevant metals. The combined data suggest that despite a high degree of sequence similarity between each HX3HXnE motif in PDEs and certain metallo-endopeptidases, PDEs employ a distinct complement of residues for interacting with metals involved in catalysis.

L22 ANSWER 9 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2001070673 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11080166
TITLE: Structure and mechanism of activity of the cyclic phosphodiesterase of Appr>p, a product of the tRNA splicing reaction.
AUTHOR: Hofmann A; Zdanov A; Genschik P; Ruvinov S; Filipowicz W; Wlodawer A
CORPORATE SOURCE: Protein Structure Section, Macromolecular Crystallography Laboratory, Program in Structural Biology, NCI-Frederick, Frederick, MD 21702, USA.. hofmanna@ncifcrf.gov
SOURCE: The EMBO journal, (2000 Nov 15) Vol. 19, No. 22, pp. 6207-17.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1FSI
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 4 Jan 2001

AB The crystal structure of the cyclic phosphodiesterase (CPDase) from Arabidopsis thaliana, an enzyme involved in the tRNA splicing pathway, was determined at 2.5 A resolution. CPDase hydrolyzes ADP-ribose 1",2"-cyclic phosphate (Appr>p), a product of the tRNA splicing reaction, to the monoester ADP-ribose 1"-phosphate (Appr-1"p). The 181 amino acid protein shows a novel, bilobal arrangement of two alphabeta modules. Each lobe consists of two alpha-helices on the outer side of the molecule, framing a three- or four-stranded antiparallel beta-sheet in the core of the protein. The active site is formed at the interface of the two beta-sheets in a water-filled cavity involving residues from two H-X-T/S-X motifs. This previously noticed motif participates in coordination of a sulfate ion. A solvent-exposed surface loop (residues 100-115) is very likely to play a flap-like role, opening and closing the active site. Based on the crystal structure and on recent mutagenesis studies of a homologous CPDase from Saccharomyces cerevisiae, we propose an enzymatic mechanism that employs the nucleophilic attack of a water molecule activated by one of the active site histidines.

L22 ANSWER 10 OF 13 MEDLINE on STN
ACCESSION NUMBER: 2000307914 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10846163
TITLE: Atomic structure of PDE4: insights into phosphodiesterase mechanism and specificity.
AUTHOR: Xu R X; Hassell A M; Vanderwall D; Lambert M H; Holmes W D; Luther M A; Rocque W J; Milburn M V; Zhao Y; Ke H; Nolte R T
CORPORATE SOURCE: Department of Structural Chemistry, Department of Molecular Sciences, Glaxo Wellcome Research and Development, Research Triangle Park, NC 27709, USA.
CONTRACT NUMBER: AI33072 (NIAID)
SOURCE: Science, (2000 Jun 9) Vol. 288, No. 5472, pp. 1822-5.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1F0J
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 6 Jul 2000
Entered Medline: 29 Jun 2000

AB Cyclic nucleotides are second messengers that are essential in vision, muscle contraction, neurotransmission, exocytosis, cell growth, and differentiation. These molecules are

degraded by a family of enzymes known as phosphodiesterases, which serve a critical function by regulating the intracellular concentration of cyclic nucleotides. We have determined the three-dimensional structure of the catalytic domain of phosphodiesterase 4B2B to 1.77 angstrom resolution. The active site has been identified and contains a cluster of two metal atoms. The structure suggests the mechanism of action and basis for specificity and will provide a framework for structure-assisted drug design for members of the phosphodiesterase family.

L22 ANSWER 11 OF 13 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:320116 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100320116
TITLE: Identification of interaction sites of cyclic nucleotide phosphodiesterase type 3A with milrinone and cilostazol.
AUTHOR(S): Zhang, Wei [Reprint author]; Jameson, Bradford A.; Ke, Hengming; Colman, Robert W. [Reprint author]
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA, USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 625a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jul 2001
Last Updated on STN: 19 Feb 2002

AB Platelet cGMP-inhibited cAMP phosphodiesterase (PDE3A) which hydrolyzes cAMP to 5' AMP has been a target for development of therapeutic agents. Currently, there are two PDE3 type-specific inhibitors that are clinically used. One, milrinone, is beneficial in selected patients with heart failure while the other, cilostazol, is a novel potent antiplatelet agent recently approved by the FDA for treatment of intermittent claudication. However, little has been known about the molecular interactions between each inhibitor and the enzyme. To identify such amino acid residues of PDE3A responsible for inhibition, we have utilized a molecular model of the catalytic domain of PDE3A based on the crystal structure of PDE4B. We have mutated nine amino acids to alanine using site-directed mutagenesis, expressed the mutants in a baculovirus/Sf9 cell system, and analyzed the kinetic characteristics of inhibition of the mutant enzyme by milrinone and cilostazol. Certain mutants displayed differential sensitivity to the distinct PDE3 type-specific inhibitors. Mutants Y751A, H840A, D950A and F1004A reduced sensitivity to milrinone (the values of IC50 were from 11.4 to >50 muM, compared with 1.98 muM of the recombinant PDE3A). The same mutants exhibited diminished sensitivity to cilostazol (the values of IC50 of the mutants were 20- to 100-fold higher than that of the recombinant PDE3A). In addition, these same mutants had an increased Ki for cGMP, a competitive inhibitor of PDE3A. By contrast, mutants T844A, F972A and Q975A showed decreased inhibition to cilostazol but no difference for the recombinant PDE3A with milrinone. Mutant F1004A showed 12-fold increase Km for cAMP while the other mutants Y751A, H840A, D950A, T844A, F972A and Q975A had normal or slightly high Km for cAMP. These results suggested that the amino acid residues that interact with the PDE3 type-specific inhibitors are shared while others are distinct. Specific amino acid residues preferentially interact with inhibitory drugs without affecting substrate interaction. Highly conserved amino acid residues (H840, D950 and F1004) in the cyclic nucleotide phosphodiesterase family participated in the interaction with PDE3A inhibitors. Detailed knowledge of the structure of the inhibitory sites should contribute to the development of more potent and specific inhibitory drugs.

L22 ANSWER 12 OF 13 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:208528 SCISEARCH Full-text
THE GENUINE ARTICLE: ZB597
TITLE: Potential roles of conserved amino acids in the catalytic domain of the cGMP-binding cGMP-specific phosphodiesterase (PDE5)
AUTHOR: Turko I V; Francis S H; Corbin J D (Reprint)
CORPORATE SOURCE: Vanderbilt Univ, Dept Mol Physiol & Biophys, Sch Med, Nashville, TN 37232 USA (Reprint)

COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (13 MAR 1998) Vol. 273, No. 11, pp. 6460-6466.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 35
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The known mammalian 3':5'-cyclic nucleotide phosphodiesterases (PDEs) contain a conserved region located toward the carboxyl terminus, which constitutes a catalytic domain, To identify amino acids that are important for catalysis, we introduced substitutions at 23 conserved residues within the catalytic domain of the cGMP-binding cGMP-specific phosphodiesterase (cGBPDE; PDES). Wild-type and mutant proteins were compared with respect to K-m for cGMP, k(cat) and IC50 for zaprinast, The most dramatic decrease in k(cat) was seen with H643A and D754A mutants with the decrease in free energy of binding (Delta Delta G(T)) being about 4.5 kcal/mol for each, which is within the range predicted for loss of a hydrogen bond involving a charged residue, His(643)?S and Asp(754) conserved in all known PDEs and are sarong candidates to be directly involved in catalysis, Substitutions of His(603), His(607), His(647), Glu(672), Asp(714) also produced marked changes in k(cat) and these residues are likely to be important for efficient catalysis, The Y602A and E775A mutants exhibited the most dramatic increases in K-m for cGAMP, with calculated Delta Delta G(T) of 2.9 and 2.8 kcaj/mol, respectively, that these two residues are important for cGMP binding in the catalytic site, Zaprinast is a potent competitive inhibitor of cGB-PDE, but the key residues for its binding differ significantly from those that bind cGMP.

L22 ANSWER 13 OF 13 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1993:499314 BIOSIS Full-text
DOCUMENT NUMBER: PREV199396123321
TITLE: Molecular cloning of the rat adipocyte hormone-sensitive cyclic GMP-inhibited cyclic nucleotide phosphodiesterase.
AUTHOR(S): Taira, Masato [Reprint author]; Hockman, Steven C.; Calvo, Juan C.; Taira, Masanori; Belfrage, Per; Manganiello, Vincent C.
CORPORATE SOURCE: Room 5N-307, Build. 10, Natl. Inst. Health, Bethesda, MD 20892, USA
SOURCE: Journal of Biological Chemistry, (1993) Vol. 268, No. 25, pp. 18573-18579.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 1993
Last Updated on STN: 6 Nov 1993

AB Two distinct but related cGMP-inhibited cyclic nucleotide phosphodiesterase (cGI PDE) cDNAs were cloned from rat adipose tissue cDNA libraries. The open reading frame (3324 base pairs) of RcGIP1 encodes 1108 amino acids, including a hydrophobic membrane-association domain in the NH-2-terminal portion and, in the COOH-terminal portion, a putative catalytic domain conserved among all mammalian PDEs which is preceded by a putative regulatory domain that contains three consensus cAMP-dependent protein kinase phosphorylation sites and followed by a hydrophilic COOH-terminal domain. The carboxyl-terminal portion including the conserved domain was expressed as a glutathione S-transferase fusion protein and exhibited cAMP PDE activity which was inhibited by cilostamide, a specific cGI PDE inhibitor. RcGIP1 cDNA hybridizes strongly with RNA from isolated adipocytes, and its mRNA increases dramatically during differentiation of 3T3-L1 adipocytes. The deduced sequence of the second partial cDNA clone (RcGIP2 clone 53B) is highly homologous to the corresponding region of human cardiac cGI PDE cDNA. RcGIP2 cDNA hybridized strongly with rat cardiac tissue RNA and weakly if at all with RNA from rat adipocytes or 3T3-L1 fibroblasts or adipocytes. We suggest that RcGIP1 represents the hormone-sensitive, membrane-associated rat adipocyte cGI PDE and RcGIP2, a cGI PDE from vascular elements in rat adipose tissue.

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=> d his

     (FILE 'HOME' ENTERED AT 11:06:41 ON 22 JUN 2006)

     FILE 'MEDLINE, CAPLUS, SCISEARCH, LIFESCI, BIOSIS, EMBASE' ENTERED AT
     11:06:57 ON 22 JUN 2006
L1            58 FILE MEDLINE
L2            52 FILE CAPLUS
L3            60 FILE SCISEARCH
L4            12 FILE LIFESCI
L5            21 FILE BIOSIS
L6            23 FILE EMBASE
     TOTAL FOR ALL FILES
L7           226 S (CYCLIC NUCLEOTIDE PHOSPHODIESTERASE OR PDE1B) AND (CRYSTAL O
L8            38 FILE MEDLINE
L9            27 FILE CAPLUS
L10           32 FILE SCISEARCH
L11            8 FILE LIFESCI
L12           14 FILE BIOSIS
L13           14 FILE EMBASE
     TOTAL FOR ALL FILES
L14          133 S L7 NOT 2004-2006/PY
L15            8 FILE MEDLINE
L16            4 FILE CAPLUS
L17            7 FILE SCISEARCH
L18            1 FILE LIFESCI
L19            6 FILE BIOSIS
L20            4 FILE EMBASE
     TOTAL FOR ALL FILES
L21           30 S L14 AND CATALYTIC DOMAIN
L22           13 DUP REM L21 (17 DUPLICATES REMOVED)

=> s (3',5'-cyclic nucleotide phosphodiesterase or PDE1B) and (crystal or X-ray)
L23           44 FILE MEDLINE
L24           15 FILE CAPLUS
L25            6 FILE SCISEARCH
L26            6 FILE LIFESCI
L27            3 FILE BIOSIS
L28            2 FILE EMBASE

TOTAL FOR ALL FILES
L29           76 (3',5'-CYCLIC NUCLEOTIDE PHOSPHODIESTERASE OR PDE1B) AND (CRYSTA
                 L OR X-RAY)

=> s l29 not 2004-2006/py
L30           29 FILE MEDLINE
L31            4 FILE CAPLUS
L32            3 FILE SCISEARCH
L33            3 FILE LIFESCI
L34            1 FILE BIOSIS
L35            1 FILE EMBASE

TOTAL FOR ALL FILES
L36           41 L29 NOT 2004-2006/PY

=> dup rem l36
PROCESSING COMPLETED FOR L36
L37           35 DUP REM L36 (6 DUPLICATES REMOVED)

=> d ibib abs 1-35

L37  ANSWER 1 OF 35  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:23015  CAPLUS Full-text
DOCUMENT NUMBER:          138:83326
TITLE:                    Proteins, druggable regions of proteins and target
                          analysis for chemistry of therapeutics
INVENTOR(S):              Edwards, Aled; Arrowsmith, Cheryl; Greenblatt, Jack;
                          Mendlein, John D.
PATENT ASSIGNEE(S):       Affinium Pharmaceuticals, Inc., Can.
SOURCE:                   PCT Int. Appl., 125 pp.
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CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003002724	A2	20030109	WO 2002-US7837	20020312
WO 2003002724	A3	20031204		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2441208	AA	20030109	CA 2002-2441208	20020312
US 2003068831	A1	20030410	US 2002-97125	20020312
US 2003068650	A1	20030410	US 2002-97193	20020312
US 2003068651	A1	20030410	US 2002-97194	20020312
PRIORITY APPLN. INFO.:			US 2001-275216P P	20010312
			WO 2002-US7837 W	20020312

AB The invention provides methods for learning structural information about a mol. or mol. complex. The invention also provides methods for identifying a compound that binds to a mol. or mol. complex. The invention also provides methods for identifying a compound that binds to one mol. or mol. complex and not to one or more other mols. or mol. complexes. Other methods that are provided can be used to identify a compound that binds to at least two mols. or mol. complexes.

L37 ANSWER 2 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003573643 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14609333
TITLE: The crystal structure of AMP-bound PDE4 suggests a mechanism for phosphodiesterase catalysis.
AUTHOR: Huai Qing; Colicelli John; Ke Hengming
CORPORATE SOURCE: Department of Biochemistry and Biophysics and Lineberger Comprehensive Cancer Center, The University of North Carolina, Chapel Hill, North Carolina 27599-7260, USA.
CONTRACT NUMBER: GM59791 (NIGMS)
NS31911 (NINDS)
SOURCE: Biochemistry, (2003 Nov 18) Vol. 42, No. 45, pp. 13220-6.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1PTW
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 16 Dec 2003
Last Updated on STN: 5 Mar 2004
Entered Medline: 4 Mar 2004

AB Cyclic nucleotide phosphodiesterases (PDEs) regulate the intracellular concentrations of cyclic 3',5'-adenosine and guanosine monophosphates (cAMP and cGMP, respectively) by hydrolyzing them to AMP and GMP, respectively. Family-selective inhibitors of PDEs have been studied for treatment of various human diseases. However, the catalytic mechanism of cyclic nucleotide hydrolysis by PDEs has remained unclear. We determined the crystal structure of the human PDE4D2 catalytic domain in complex with AMP at 2.4 A resolution. In this structure, two divalent metal ions simultaneously interact with the phosphate group of AMP, implying a binuclear catalysis. In addition, the structure suggested that a hydroxide ion or a water bridging two metal ions may serve as the nucleophile for the hydrolysis of the cAMP phosphodiester bond.

L37 ANSWER 3 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003543982 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14622266

TITLE: Characterization of Met95 mutants of a heme-regulated phosphodiesterase from Escherichia coli. Optical absorption, magnetic circular dichroism, circular dichroism, and redox potentials.
AUTHOR: Hirata Satoshi; Matsui Toshitaka; Sasakura Yukie; Sugiyama Shunpei; Yoshimura Tokiko; Sagami Ikuko; Shimizu Toru
CORPORATE SOURCE: Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, Sendai, Japan.
SOURCE: European journal of biochemistry / FEBS, (2003 Dec) Vol. 270, No. 23, pp. 4771-9.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 6 Jan 2004
Entered Medline: 5 Jan 2004

AB On the basis of amino acid sequences and crystal structures of similar enzymes, it is proposed that Met95 of the heme-regulated phosphodiesterase from Escherichia coli (Ec DOS) acts as a heme axial ligand. In accordance with this proposal, the Soret and visible optical absorption and magnetic circular dichroism spectra of the Fe(II) complexes of the Met95Ala and Met95Leu mutant proteins indicate that these complexes are five-coordinated high-spin, suggesting that Met95 is an axial ligand for the Fe(II) complex. However, the Fe(III) complexes of these mutants are six-coordinated low-spin, like the wild-type enzyme. The latter spectral findings are inconsistent with the proposal that the axial ligand to the Fe(III) heme is Met95. To determine the possibility of a redox-dependent ligand switch in Ec DOS, we further analyzed Soret CD spectra and redox potentials, which provide direct evidence on the environmental structure of the heme protein. CD spectra of Fe(III) Met95 mutants were all different from those of the wild-type protein, suggesting indirect coordination of Met95 to the Fe(III) wild-type heme. The redox potentials of the Met95Leu, Met95Ala and Met95His mutants were considerably lower than that of the wild-type enzyme (+70 mV) at -1, -26, and -122 mV vs. SHE, respectively. Thus, it is reasonable to speculate that water (or hydroxy anion) interacting with Met95, rather than Met95 itself, is the axial ligand to the Fe(III) heme.

L37 ANSWER 4 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003263745 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12773045
TITLE: Optimization of a tertiary alcohol series of phosphodiesterase-4 (PDE4) inhibitors: structure-activity relationship related to PDE4 inhibition and human ether-a-go-go related gene potassium channel binding affinity.
AUTHOR: Friesen Richard W; Ducharme Yves; Ball Richard G; Blouin Marc; Boulet Louise; Cote Bernard; Frenette Richard; Girard Mario; Guay Daniel; Huang Zheng; Jones Thomas R; Laliberte France; Lynch Joseph J; Mancini Joseph; Martins Evelyn; Masson Paul; Muise Eric; Pon Douglas J; Siegl Peter K S; Styhler Angela; Tsou Nancy N; Turner Mervyn J; Young Robert N; Girard Yves
CORPORATE SOURCE: Department of Biology and Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, Quebec, H9R 4P8, Canada..
rick_friesen@merck.com
SOURCE: Journal of medicinal chemistry, (2003 Jun 5) Vol. 46, No. 12, pp. 2413-26.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 8 Jun 2003
Last Updated on STN: 13 Jul 2003
Entered Medline: 11 Jul 2003

AB A SAR study on the tertiary alcohol series of phosphodiesterase-4 (PDE4) inhibitors related to 1 is described. In addition to inhibitory potency against PDE4 and the lipopolysaccharide-induced production of TNFalpha in human whole blood, the binding

affinity of these compounds for the human ether-a-go-go related gene (hERG) potassium channel (an in vitro measure for the potential to cause QTc prolongation) was assessed. Four key structural moieties in the molecule were studied, and the impact of the resulting modifications in modulating these activities was evaluated. From these studies, (+)-3d (L-869,298) was identified as an optimized structure with respect to PDE4 inhibitory potency, lack of binding affinity to the hERG potassium channel, and pharmacokinetic behavior. (+)-3d exhibited good in vivo efficacy in several models of pulmonary function with a wide therapeutic index with respect to emesis and prolongation of the QTc interval.

L37 ANSWER 5 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003346036 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12878217
TITLE: The role of tryptophan 1072 in human PDE3B inhibitor binding.
AUTHOR: Chung Christine; Varnerin Jeffrey P; Morin Nancy R; MacNeil Douglas J; Singh Suresh B; Patel Sangita; Scapin Giovanna; Van der Ploeg Lex H T; Tota Michael R
CORPORATE SOURCE: Department of Metabolic Disorders, Merck Research Laboratories, P.O. Box 2000, Mailstop: RY80M-213, Rahway, NJ 07065, USA.
SOURCE: Biochemical and biophysical research communications, (2003 Aug 8) Vol. 307, No. 4, pp. 1045-50.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 25 Jul 2003
Last Updated on STN: 13 Sep 2003
Entered Medline: 12 Sep 2003

AB The catalytic domain of recombinant human PDE3B was expressed in Escherichia coli as inclusion bodies and refolded to form active enzyme. A mutation at tryptophan 1072 in PDE3B disrupts inhibitor binding, but has minimal effect on cAMP hydrolysis. The W1072A mutation caused a 158-fold decrease in affinity for cilostamide, a 740-fold decrease for cGMP, and a 15-fold decrease in affinity for IBMX. The corresponding tyrosine mutation had a smaller effect. However, the K(m) of cAMP for the W1072A mutation was only increased by about 7-fold. The data indicate that the inhibitor binding region is not completely coincident with the substrate binding region. The homologous residue in PDE4B is located on helix 16 within 7A of the predicted bound substrate. A model of PDE3B was constructed based on the X-ray crystal structure of PDE4B.

L37 ANSWER 6 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003315344 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12842049
TITLE: Three-dimensional structures of PDE4D in complex with roliprams and implication on inhibitor selectivity.
AUTHOR: Huai Qing; Wang Huanchen; Sun Yingjie; Kim Hwa-Young; Liu Yudong; Ke Hengming
CORPORATE SOURCE: Department of Biochemistry and Biophysics and Lineberger Comprehensive Cancer Center, The University of North Carolina, Chapel Hill, Chapel Hill, NC 27599, USA.
CONTRACT NUMBER: GM59791 (NIGMS)
SOURCE: Structure (Cambridge, Mass. : 2001), (2003 Jul) Vol. 11, No. 7, pp. 865-73.
Journal code: 101087697. ISSN: 0969-2126.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1OYM; PDB-1OYN
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 8 Jul 2003
Last Updated on STN: 20 Mar 2004
Entered Medline: 19 Mar 2004

AB Selective inhibitors against the 11 families of cyclic nucleotide phosphodiesterases (PDEs) are used to treat various human diseases. How the inhibitors selectively bind the conserved PDE catalytic domains is unknown. The crystal structures of the PDE4D2 catalytic domain in complex with (R)- or (R,S)-rolipram suggest that inhibitor selectivity

is determined by the chemical nature of amino acids and subtle conformational changes of the binding pockets. The conformational states of Gln369 in PDE4D2 may play a key role in inhibitor recognition. The corresponding Y329S mutation in PDE7 may lead to loss of the hydrogen bonds between rolipram and Gln369 and is thus a possible reason explaining PDE7's insensitivity to rolipram inhibition. Docking of the PDE5 inhibitor sildenafil into the PDE4 catalytic pocket further helps understand inhibitor selectivity.

L37 ANSWER 7 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2003136910 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12650945
TITLE: Modeling and mutational analysis of the GAF domain of the cGMP-binding, cGMP-specific phosphodiesterase, PDE5.
AUTHOR: Sopory Shailaja; Balaji S; Srinivasan N; Visweswariah Sandhya S
CORPORATE SOURCE: Department of Molecular Reproduction, Development and Genetics, Indian Institute of Science, 560012 Bangalore, India.
SOURCE: FEBS letters, (2003 Mar 27) Vol. 539, No. 1-3, pp. 161-6. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 25 Mar 2003
Last Updated on STN: 25 Apr 2003
Entered Medline: 24 Apr 2003

AB The GAFa domain of the cGMP-binding, cGMP-specific phosphodiesterase (PDE5A) was modeled on the crystal structure of PDE2A GAF domain and residues involved in cGMP binding identified. Tandem GAFa and GAFb domains of PDE5A, expressed in Escherichia coli, bound cGMP (K(d) 27 nM). Mutation of aspartate-299 in GAFa, suggested earlier to be critical for cGMP binding, did not abrogate cGMP binding, but mutation of F205, which formed a stacking interaction with the guanine ring of cGMP, led to complete loss of cGMP binding. Therefore, the GAFa domain of PDE5A adopts a structure similar to the GAFb domain of PDE2A, and provides the sole site for cGMP binding in PDE5A.

L37 ANSWER 8 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002498734 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12271124
TITLE: The two GAF domains in phosphodiesterase 2A have distinct roles in dimerization and in cGMP binding.
AUTHOR: Martinez Sergio E; Wu Albert Y; Glavas Natalie A; Tang Xiao-Bo; Turley Stewart; Hol Wim G J; Beavo Joseph A
CORPORATE SOURCE: Departments of Pharmacology, and Biochemistry and Biological Structure, Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195, USA.
CONTRACT NUMBER: DK 21723 (NIDDK)
HL44948 (NHLBI)
T32 HL07312-23 (NHLBI)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 Oct 1) Vol. 99, No. 20, pp. 13260-5. Electronic Publication: 2002-09-23. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1MC0
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 3 Oct 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 13 Nov 2002

AB Cyclic nucleotide phosphodiesterases (PDEs) regulate all pathways that use cGMP or cAMP as a second messenger. Five of the 11 PDE families have regulatory segments containing GAF domains, 3 of which are known to bind cGMP. In PDE2 binding of cGMP to the GAF domain causes an activation of the catalytic activity by a mechanism that apparently is shared even in the adenylyl cyclase of Anabaena, an organism separated from mouse by 2 billion years of evolution. The 2.9-A crystal structure of the mouse PDE2A regulatory segment reported in this paper reveals that the GAF A domain functions as a dimerization locus.

The GAF B domain shows a deeply buried cGMP displaying a new cGMP-binding motif and is the first atomic structure of a physiological cGMP receptor with bound cGMP. Moreover, this cGMP site is located well away from the region predicted by previous mutagenesis and structural genomic approaches.

L37 ANSWER 9 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002309211 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12036361
TITLE: Novel selective phosphodiesterase (PDE4) inhibitors. 4. Resolution, absolute configuration, and PDE4 inhibitory activity of cis-tetra- and cis-hexahydrophthalazinones.
AUTHOR: Van der Mey Margaretha; Boss Hildegard; Couwenberg Dennis; Hatzelmann Armin; Sterk Geert J; Goubitz Kees; Schenk Henk; Timmerman Hendrik
CORPORATE SOURCE: Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1085c, 1081 HV Amsterdam, The Netherlands.. mmeij@rnc.vu.nl
SOURCE: Journal of medicinal chemistry, (2002 Jun 6) Vol. 45, No. 12, pp. 2526-33.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 11 Jun 2002
Last Updated on STN: 28 Jun 2002
Entered Medline: 27 Jun 2002

AB Recently, we reported that 4-catechol-substituted cis-(+/-)-4a,5,6,7,8,8a- hexa- and cis-(+/-)-4a,5,8,8a-tetrahydro-2H-phthalazin-1-ones show potent inhibition of phosphodiesterase (PDE4) activity, while the corresponding trans racemic mixtures exhibit only weak to moderate activity. To determine the absolute configuration and PDE4 inhibitory activity of the individual cis-enantiomers, several optically active phthalazinones have been synthesized. The enantiomers of the various gamma-keto acids, used as starting materials, were resolved in a classical way by the formation of diastereomeric salts, and each was converted to optically active phthalazinone in an enantioselective manner. The absolute configuration of the (+)-enantiomer of cis-hexahydrophthalazinone (+)-12 was determined by X-ray crystallography. The carbon atoms at the 4a and 8a positions were found to have the S- and R-configuration, respectively. In the present series of hexa- and tetrahydrophthalazinones, stereoselectivity for PDE4 inhibition is observed; the cis-(+)-enantiomers of the phthalazinones display high inhibitory activity, whereas their (-)-counterparts exhibit only weak to moderate activity. It is likely that all cis-(+)-phthalazinones have a (4aS,8aR)-configuration and vice versa for the cis-(-)-analogues. In the current series, the N-adamantan-2-yl analogue (+)-14 shows the most potent inhibition of PDE4 (pIC(50) = 9.3); the corresponding (-)-enantiomer is 250-fold less active. In addition, the N-substituted tetrahydrophthalazinones under study were investigated for their in vivo antiinflammatory activities by examining the suppression of arachidonic acid (AA) induced mouse ear edema formation. In this assay analogues (+)-14 and (+)-15 were found to be potent antiinflammatory agents showing about 50% inhibition at 30 micromol/kg po.

L37 ANSWER 10 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002054089 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11694509
TITLE: Crystal structures of the semireduced and inhibitor-bound forms of cyclic nucleotide phosphodiesterase from Arabidopsis thaliana.
AUTHOR: Hofmann Andreas; Grella Melissa; Botos Istvan; Filipowicz Witold; Wlodawer Alexander
CORPORATE SOURCE: Macromolecular Crystallography Laboratory, NCI, National Institutes of Health, Frederick, Maryland 21702, USA.. hofmanna@ncifcrf.gov
SOURCE: The Journal of biological chemistry, (2002 Jan 11) Vol. 277, No. 2, pp. 1419-25. Electronic Publication: 2001-11-01.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1JH6; PDB-1JH7
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 7 Feb 2002

AB The crystal structure of the semireduced form of cyclic nucleotide phosphodiesterase (CPDase) from Arabidopsis thaliana has been solved by molecular replacement and refined at the resolution of 1.8 A. We have previously reported the crystal structure of the native form of this enzyme, whose main target is ADP-ribose 1",2"-cyclic phosphate, a product of the tRNA splicing reaction. CPDase possesses six cysteine residues, four of which are involved in forming two intra-molecular disulfide bridges. One of these bridges, between Cys-104 and Cys-110, is opened in the semireduced CPDase, whereas the other remains intact. This change of the redox state leads to a conformational rearrangement in the loop covering the active site of the protein. While the native structure shows this partially disordered loop in a coil conformation, in the semireduced enzyme the N-terminal lobe of this loop winds up and elongates the preceding alpha-helix. The semireduced state of CPDase also enabled co-crystallization with a putative inhibitor of its enzymatic activity, 2',3'-cyclic uridine vanadate. The ligand is bound within the active site, and the mode of binding is in agreement with the previously proposed enzymatic mechanism. Selected biophysical properties of the oxidized and the semireduced CPDase are also discussed.

L37 ANSWER 11 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002437990 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12181427
TITLE: Identification of interaction sites of cyclic nucleotide phosphodiesterase type 3A with milrinone and cilostazol using molecular modeling and site-directed mutagenesis.
AUTHOR: Zhang W; Ke H; Colman R W
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
CONTRACT NUMBER: P01-HL64943 (NHLBI)
R01-GM59791 (NIGMS)
SOURCE: Molecular pharmacology, (2002 Sep) Vol. 62, No. 3, pp. 514-20.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 29 Aug 2002
Last Updated on STN: 6 Sep 2002
Entered Medline: 5 Sep 2002

AB To identify amino acid residues involved in PDE3-selective inhibitor binding, we selected eight presumed interacting residues in the substrate-binding pocket of PDE3A using a model created on basis of homology to the PDE4B crystal structure. We changed the residues to alanine using site-directed mutagenesis technique, expressed the mutants in a baculovirus/Sf9 cell system, and analyzed the kinetic characteristics of inhibition of the mutant enzymes by milrinone and cilostazol, specific inhibitors of PDE3. The mutants displayed differential sensitivity to the inhibitors. Mutants Y751A, D950A, and F1004A had reduced sensitivity to milrinone (K(i) changed from 0.66 microM for the recombinant PDE3A to 7.5 to 156 microM for the mutants), and diminished sensitivity to cilostazol (K(i) of the mutants were 18- to 371-fold higher than that of the recombinant PDE3A). In contrast, the mutants T844A, F972A and Q975A showed increased K(i) for cilostazol but no difference for milrinone from the recombinant PDE3A. Molecular models show that the PDE3 inhibitors cilostazol and milrinone share some of common residues but interact with distinct residues at the active site, suggesting that selective inhibitors can be designed with flexible size against PDE3 active site. Our study implies that highly conserved residuals Y751, D950 and F1004 in the PDE families are key residues for binding of both substrate and inhibitors, and nonconserved T844 may be responsible for the cilostazol selectivity of PDE3A. Detailed knowledge of the structure of inhibitory sites should contribute to development of more potent and specific inhibitory drugs.

L37 ANSWER 12 OF 35 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:135593 SCISEARCH Full-text
THE GENUINE ARTICLE: 518CE
TITLE: 3 ',5 '-cyclic nucleotide phosphodiesterases class III: Members, structure, and catalytic mechanism
AUTHOR: Richter W (Reprint)
CORPORATE SOURCE: Stanford Univ, Sch Med, Div Reprod Biol, Dept Gynecol & Obstet, 300 Pasteur Dr, Stanford, CA 94305 USA (Reprint); Stanford Univ, Sch Med, Div Reprod Biol, Dept Gynecol & Obstet, Stanford, CA 94305 USA
COUNTRY OF AUTHOR: USA
SOURCE: PROTEINS-STRUCTURE FUNCTION AND GENETICS, (15 FEB 2002) Vol. 46, No. 3, pp. 278-286. ISSN: 0887-3585.
PUBLISHER: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 44
ENTRY DATE: Entered STN: 22 Feb 2002
Last Updated on STN: 22 Feb 2002

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB 3',5'-Cyclic nucleotide phosphodiesterases (PDEs) comprise a superfamily of enzymes that were previously divided by their primary structure into two major classes: PDE class I and II. The 3',5'-cyclic AMP phosphodiesterase from Escherichia coli encoded by the cpdA gene does not show any homology to either PDE class I or class II enzymes and, therefore, represents a new, third class of PDEs. Previously, information about essential structural elements, substrate and cofactor binding sites, and the mechanism of catalysis was unknown for this enzyme. The present study shows by computational analysis that the enzyme encoded by the E. coli cpdA gene belongs to a family of phosphodiesterases that closely resembles the catalytic machinery known from purple acid phosphatases and several other dimetallophosphoesterases. They share both the conserved sequence motif, D-(X)(n)-GD-(X)(n)-GNH[E/D]-(X)(n)-H-(X)(n) -GHXH, which contains the invariant residues forming the active site of purple acid phosphatases, a binuclear Fe3+-Me2+-containing center, as well as a betaalphabetaalphabeta motif as a typical secondary structure signature. Furthermore, the known biochemical properties of the bacterial phosphodiesterase encoded by the cpdA gene, such as the requirement of iron ions and a reductant for maintaining its catalytic activity, support this hypothesis developed by computational analysis. In addition, the availability of atomic coordinates for several purple acid phosphatases and related proteins allowed the generation of a three-dimensional model for class III cyclic nucleotide phosphodiesterases. (C) 2002 Wiley-Liss, Inc.

L37 ANSWER 13 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002740099 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12503612
TITLE: Methodology and problems of protein-ligand docking: case study of dihydroorotate dehydrogenase, thymidine kinase, and phosphodiesterase 4.
AUTHOR: Pospisil Pavel; Kuoni Thomas; Scapozza Leonardo; Folkers Gerd
CORPORATE SOURCE: Department of Applied Biosciences, Swiss Federal Institute of Technology (ETH) Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.
SOURCE: Journal of receptor and signal transduction research, (2002 Feb-Nov) Vol. 22, No. 1-4, pp. 141-54. Journal code: 9509432. ISSN: 1079-9893.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 31 Dec 2002
Last Updated on STN: 6 Jun 2003
Entered Medline: 5 Jun 2003

AB The docking methodology was applied to three different therapeutically interesting enzymes: human dihydroorotate dehydrogenase (DHODH), Herpes simplex virus type I thymidine kinase (HSV1 TK) and human phosphodiesterase 4 (PDE4). Programs FlexX, AutoDock and DOCK where used. The three targets represent three distinct cases. For DHODH and HSV1 TK, the

binding modes of substrate and inhibitors within the active site are known, while the binding orientation of cAMP within PDE4 has been solely hypothesized. Active site of DHODH is mainly hydrophobic and the binding mode of the inhibitor brequinar was used as a template for evaluating the docking strategies. The presence of cofactors revealed to be crucial for the definition of the docking site. The HSV1 TK active site is small and polar and contains crystal water molecules and ATP. Docking of thymidine and aciclovir (ACV) within the active site was analyzed by keeping or removing water molecules. It showed the crucial role of water in predicting the binding of pyrimidines and purines. The crystal structure of PDE4 contains magnesium and zinc cations as well as catalytic water molecule but no ligand. Several docking experiments of cAMP and rolipram were performed and the results showed clear-cut dependence between the ligand orientation and the presence of metals in the active site. All three cases show specific problems of the docking methodology, depending on the character of the active site.

L37 ANSWER 14 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002630336 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12387865
TITLE: Crystal structure of phosphodiesterase 4D and inhibitor complex(1).
AUTHOR: Lee Mi Eun; Markowitz Joseph; Lee Jie Oh; Lee Hayyoung
CORPORATE SOURCE: Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1 Kusong-dong, Yusong-gu, Daejon 305-701, South Korea.
SOURCE: FEBS letters, (2002 Oct 23) Vol. 530, No. 1-3, pp. 53-8. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 22 Oct 2002
Last Updated on STN: 17 Dec 2002
Entered Medline: 10 Dec 2002
AB Cyclic nucleotide phosphodiesterases (PDEs) regulate physiological processes by degrading intracellular second messengers, adenosine-3',5'-cyclic phosphate or guanosine-3',5'-cyclic phosphate. The first crystal structure of PDE4D catalytic domain and a bound inhibitor, zardaverine, was determined. Zardaverine binds to a highly conserved pocket that includes the catalytic metal binding site. Zardaverine fills only a portion of the active site pocket. More selective PDE4 inhibitors including rolipram, cilomilast and roflumilast have additional functional groups that can utilize the remaining empty space for increased binding energy and selectivity. In the crystal structure, the catalytic domain of PDE4D possesses an extensive dimerization interface containing residues that are highly conserved in PDE1, 3, 4, 8 and 9. Mutations of R358D or D322R among these interface residues prohibit dimerization of the PDE4D catalytic domain in solution.

L37 ANSWER 15 OF 35 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:334713 CAPLUS Full-text
DOCUMENT NUMBER: 135:107117
TITLE: Toward Proteomimetics: Terphenyl Derivatives as Structural and Functional Mimics of Extended Regions of an α-Helix
AUTHOR(S): Orner, Brendan P.; Ernst, Justin T.; Hamilton, Andrew D.
CORPORATE SOURCE: Department of Chemistry, Yale University, New Haven, CT, 06510-8107, USA
SOURCE: Journal of the American Chemical Society (2001), 123(22), 5382-5383
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Terphenyls 3,4-Et(3-RCH2C6H4)C6H3C6H3(CHMe2)OCH2CO2H-2,4 [I, R = Ph, 1-naphthyl, 2-naphthyl] were prepared as mimics of the α-helical domain of smooth muscle myosin light chain kinase. I [R = naphthyl] are potent inhibitors of calmodulin activation of 3',5'-cyclic nucleotide phosphodiesterase.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 16 OF 35 MEDLINE on STN

ACCESSION NUMBER: 2002026242 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11468344
TITLE: Identification of overlapping but distinct cAMP and cGMP interaction sites with cyclic nucleotide phosphodiesterase 3A by site-directed mutagenesis and molecular modeling based on crystalline PDE4B.
AUTHOR: Zhang W; Ke H; Tretiakova A P; Jameson B; Colman R W
CORPORATE SOURCE: The Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140, USA.
CONTRACT NUMBER: P01 HL64943 (NHLBI)
R01 GM59791 (NIGMS)
R01 NS37726 (NINDS)
T32 HL07777 (NHLBI)
SOURCE: Protein science : a publication of the Protein Society, (2001 Aug) Vol. 10, No. 8, pp. 1481-9.
Journal code: 9211750. ISSN: 0961-8368.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 21 Jan 2002
Last Updated on STN: 21 Jan 2002
Entered Medline: 7 Dec 2001

AB Cyclic nucleotide phosphodiesterase 3A (PDE3A) hydrolyzes cAMP to AMP, but is competitively inhibited by cGMP due to a low k(cat) despite a tight K(m). Cyclic AMP elevation is known to inhibit all pathways of platelet activation, and thus regulation of PDE3 activity is significant. Although cGMP elevation will inhibit platelet function, the major action of cGMP in platelets is to elevate cAMP by inhibiting PDE3A. To investigate the molecular details of how cGMP, a similar but not identical molecule to cAMP, behaves as an inhibitor of PDE3A, we constructed a molecular model of the catalytic domain of PDE3A based on homology to the recently determined X-ray crystal structure of PDE4B. Based on the excellent fit of this model structure, we mutated nine amino acids in the putative catalytic cleft of PDE3A to alanine using site-directed mutagenesis. Six of the nine mutants (Y751A, H840A, D950A, F972A, Q975A, and F1004A) significantly decreased catalytic efficiency, and had k(cat)/K(m) less than 10% of the wild-type PDE3A using cAMP as substrate. Mutants N845A, F972A, and F1004A showed a 3- to 12-fold increase of K(m) for cAMP. Four mutants (Y751A, H840A, D950A, and F1004A) had a 9- to 200-fold increase of K(i) for cGMP in comparison to the wild-type PDE3A. Studies of these mutants and our previous study identified two groups of amino acids: E866 and F1004 contribute commonly to both cAMP and cGMP interactions while N845, E971, and F972 residues are unique for cAMP and the residues Y751, H836, H840, and D950 interact with cGMP. Therefore, our results provide biochemical evidence that cGMP interacts with the active site residues differently from cAMP.

L37 ANSWER 17 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2002048827 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11776290
TITLE: CoMFA and CoMSIA 3D-quantitative structure-activity relationship model on benzodiazepine derivatives, inhibitors of phosphodiesterase IV.
AUTHOR: Ducrot P; Andrianjara C R; Wrigglesworth R
CORPORATE SOURCE: Pfizer Global Research and Development, Fresnes Laboratories, France.. Pierre.ducrot@pfizer.com
SOURCE: Journal of computer-aided molecular design, (2001 Sep) Vol. 15, No. 9, pp. 767-85.
Journal code: 8710425. ISSN: 0920-654X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 25 Jan 2002
Last Updated on STN: 11 Jun 2002
Entered Medline: 10 Jun 2002

AB Recently, we reported structurally novel PDE4 inhibitors based on 1,4-benzodiazepine derivatives. The main interest in developing bezodiazepine-based PDE4 inhibitors is in their lack of adverse effects of emesis with respect to rolipram-like compounds. A large effort has thus been made toward the structural optimization of this series. In the

absence of structural information on the inhibitor binding mode into the PDE4 active site, 2D-QSAR (H-QSAR) and two 3D-QSAR (CoMFA and CoMSIA) methods were applied to improve our understanding of the molecular mechanism controlling the PDE4 affinity of the benzodiazepine derivatives. As expected, the CoMSIA 3D contour maps have provided more information on the benzodiazepine interaction mode with the PDE4 active site whereas CoMFA has built the best tool for activity prediction. The 2D pharmacophoric model derived from CoMSIA fields is consistent with the crystal structure of the PDE4 active site reported recently. The combination of the 2D and 3D-QSAR models was used not only to predict new compounds from the structural optimization process, but also to screen a large library of bezodiazepine derivatives.

L37 ANSWER 18 OF 35 LIFESCI COPYRIGHT 2006 CSA on STN
ACCESSION NUMBER: 2001:19369 LIFESCI Full-text
TITLE: Structure and mechanism of activity of the cyclic phosphodiesterase of Appr>p, a product of the tRNA splicing reaction
AUTHOR: Hofmann, A.; Zdanov, A.; Genschik, P.; Ruvinov, S.; Filipowicz, W.; Wlodawer, A.
CORPORATE SOURCE: Protein Structure Section, Macromolecular Crystallography Laboratory, Program in Structural Biology, NCI-Frederick, Frederick, MD 21702, USA; E-mail: hofmanna@ncifcrf.gov
SOURCE: EMBO Journal [EMBO J.], (20001115) vol. 19, no. 22, pp. 6207-6217.
ISSN: 0261-4189.
DOCUMENT TYPE: Journal
FILE SEGMENT: N
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The crystal structure of the cyclic phosphodiesterase (CPDase) from Arabidopsis thaliana, an enzyme involved in the tRNA splicing pathway, was determined at 2.5 Aa resolution. CPDase hydrolyzes ADP-ribose 1'',2''-cyclic phosphate (Appr>p), a product of the tRNA splicing reaction, to the monoester ADP-ribose 1''- phosphate (Appr-1''p). The 181 amino acid protein shows a novel, bilobal arrangement of two alpha s modules. Each lobe consists of two alpha -helices on the outer side of the molecule, framing a three- or four-stranded antiparallel s-sheet in the core of the protein. The active site is formed at the interface of the two s-sheets in a water-filled cavity involving residues from two H-X-T/S-X motifs. This previously noticed motif participates in coordination of a sulfate ion. A solvent-exposed surface loop (residues 100-115) is very likely to play a flap-like role, opening and closing the active site. Based on the crystal structure and on recent mutagenesis studies of a homologous CPDase from Saccharomyces cerevisiae, we propose an enzymatic mechanism that employs the nucleophilic attack of a water molecule activated by one of the active site histidines.

L37 ANSWER 19 OF 35 MEDLINE on STN
ACCESSION NUMBER: 2000307914 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10846163
TITLE: Atomic structure of PDE4: insights into phosphodiesterase mechanism and specificity.
AUTHOR: Xu R X; Hassell A M; Vanderwall D; Lambert M H; Holmes W D; Luther M A; Rocque W J; Milburn M V; Zhao Y; Ke H; Nolte R T
CORPORATE SOURCE: Department of Structural Chemistry, Department of Molecular Sciences, Glaxo Wellcome Research and Development, Research Triangle Park, NC 27709, USA.
CONTRACT NUMBER: AI33072 (NIAID)
SOURCE: Science, (2000 Jun 9) Vol. 288, No. 5472, pp. 1822-5.
Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1F0J
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 6 Jul 2000
Entered Medline: 29 Jun 2000
AB Cyclic nucleotides are second messengers that are essential in vision, muscle contraction, neurotransmission, exocytosis, cell growth, and differentiation. These molecules are degraded by a family of enzymes known as phosphodiesterases, which serve a critical

function by regulating the intracellular concentration of cyclic nucleotides. We have determined the three-dimensional structure of the catalytic domain of phosphodiesterase 4B2B to 1.77 angstrom resolution. The active site has been identified and contains a cluster of two metal atoms. The structure suggests the mechanism of action and basis for specificity and will provide a framework for structure-assisted drug design for members of the phosphodiesterase family.

L37 ANSWER 20 OF 35 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:208528 SCISEARCH Full-text
THE GENUINE ARTICLE: ZB597
TITLE: Potential roles of conserved amino acids in the catalytic domain of the cGMP-binding cGMP-specific phosphodiesterase (PDE5)
AUTHOR: Turko I V; Francis S H; Corbin J D (Reprint)
CORPORATE SOURCE: Vanderbilt Univ, Dept Mol Physiol & Biophys, Sch Med, Nashville, TN 37232 USA (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (13 MAR 1998) Vol. 273, No. 11, pp. 6460-6466.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 35
ENTRY DATE: Entered STN: 1998
Last Updated on STN: 1998
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The known mammalian 3':5'-cyclic nucleotide phosphodiesterases (PDEs) contain a conserved region located toward the carboxyl terminus, which constitutes a catalytic domain, To identify amino acids that are important for catalysis, we introduced substitutions at 23 conserved residues within the catalytic domain of the cGMP-binding cGMP-specific phosphodiesterase (cGBPDE; PDES). Wild-type and mutant proteins were compared with respect to K-m for cGMP, k(cat) and IC50 for zaprinast, The most dramatic decrease in k(cat) was seen with H643A and D754A mutants with the decrease in free energy of binding (Delta Delta G(T)) being about 4.5 kcal/mol for each, which is within the range predicted for loss of a hydrogen bond involving a charged residue, His(643)?S and Asp(754) conserved in all known PDEs and are sarong candidates to be directly involved in catalysis, Substitutions of His(603), His(607), His(647), Glu(672), Asp(714) also produced marked changes in k(cat) and these residues are likely to be important for efficient catalysis, The Y602A and E775A mutants exhibited the most dramatic increases in K-m for cGAMP, with calculated Delta Delta G(T) of 2.9 and 2.8 kcaj/mol, respectively, that these two residues are important for cGMP binding in the catalytic site, Zaprinast is a potent competitive inhibitor of cGB-PDE, but the key residues for its binding differ significantly from those that bind cGMP.

L37 ANSWER 21 OF 35 MEDLINE on STN
ACCESSION NUMBER: 1999042020 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9822544
TITLE: Synthesis of 7-benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridine and novel derivatives free of positional isomers. Potent inhibitors of cAMP-specific phosphodiesterase and of malignant tumor cell growth.
AUTHOR: Merz K H; Marko D; Regiert T; Reiss G; Frank W; Eisenbrand G
CORPORATE SOURCE: Departments of Chemistry, Division of Food Chemistry and Environmental Toxicology and Division of Inorganic Chemistry, University of Kaiserslautern, Germany.
SOURCE: Journal of medicinal chemistry, (1998 Nov 19) Vol. 41, No. 24, pp. 4733-43.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999

Last Updated on STN: 15 Jan 1999
Entered Medline: 17 Dec 1998

AB 7-Benzylamino-6-chloro-2-piperazino-4-pyrrolidinopteridine (7a) is a potent inhibitor of the cAMP-specific phosphodiesterase isoenzyme family PDE4 and induces growth inhibition in a panel of tumor cell lines. In this study, we describe a synthesis that yields 7a and novel derivatives free of positional isomers. The synthesis of alkylamino substituted pteridines is based on the successive nucleophilic aromatic substitution of the chlorine atoms of 2,4,6, 7-tetrachloropteridine. For the reaction with secondary amines, the positional order of reactivity was found to be C4 > C7 > C2 > C6. Final structural proof is given by X- ray crystallography. To unravel structural elements of 7a crucial for the interaction with the target enzyme, the compound was modified systematically. The impact of the modifications on activity was tested by evaluating the ability of the compounds to inhibit cAMP hydrolysis by cAMP-specific phosphodiesterase (PDE4) purified from the solid human large cell lung tumor xenograft LXFL529. Growth inhibitory properties were determined by in vitro treatment of the respective cell line LXFL529L using the sulforhodamine B assay (SRB). The results show that for high activity, the heterocyclic substituent in position 2 of the pteridine ring system requires the presence of a basic nitrogen in 4'-position, as represented by piperazine.

L37 ANSWER 22 OF 35 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 96392399 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8799187
TITLE: Direct modulation of calmodulin targets by the neuronal calcium sensor NCS-1.
AUTHOR: Schaad N C; De Castro E; Nef S; Hegi S; Hinrichsen R; Martone M E; Ellisman M H; Sikkink R; Rusnak F; Sygush J; Nef P
CORPORATE SOURCE: Department of Biochemistry, University of Geneva, Switzerland.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1996 Aug 20) Vol. 93, No. 17, pp. 9253-8.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 6 Feb 1998
Entered Medline: 31 Oct 1996

AB Ca2+ and its ubiquitous intracellular receptor calmodulin (CaM) are required in the nervous system, among a host of cellular responses, for the modulation of several important enzymes and ion channels involved in synaptic efficacy and neuronal plasticity. Here, we report that CaM can be replaced by the neuronal calcium sensor NCS-1 both in vitro and in vivo. NCS-1 is a calcium binding protein with two Ca(2+)-binding domains that shares only 21% of homology with CaM. We observe that NCS-1 directly activates two Ca2+/CaM-dependent enzymes (3':5'- cyclic nucleotide phosphodiesterase and protein phosphatase calcineurin). Co-activation of nitric oxide synthase by NCS-1 and CaM results in a higher activity than with CaM alone. Moreover, NCS-1 is coexpressed with calcineurin and nitric oxide synthase in several neuron populations. Finally, injections of NCS-1 into calmodulin-defective cam1 Paramecium partially restore wildtype behavioral responses. With this highly purified preparation of NCS-1, we have obtained crystals suitable for crystallographic structure studies. NCS-1, despite its very different structure, distribution, and Ca(2+)-binding affinity as compared with CaM, can substitute for or potentiate CaM functions. Therefore, NCS-1 represents a novel protein capable of mediating multiple Ca(2+)-signaling pathways in the nervous system.

L37 ANSWER 23 OF 35 MEDLINE on STN
ACCESSION NUMBER: 96405016 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8809156
TITLE: Synthesis and cardiotonic activity of novel pyrimidine derivatives: crystallographic and quantum chemical studies.
AUTHOR: Dorigo P; Fraccarollo D; Santostasi G; Maragno I; Floreani M; Borea P A; Mosti L; Sansebastiano L; Fossa P; Orsini F; Benetollo F; Bombieri G
CORPORATE SOURCE: Dipartimento di Farmacologia, Universita di Padova, Italy.
SOURCE: Journal of medicinal chemistry, (1996 Sep 13) Vol. 39, No. 19, pp. 3671-83.

Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19 Dec 1996
Last Updated on STN: 29 Jan 1999
Entered Medline: 4 Nov 1996

AB The synthesis of ethyl or methyl 4-substituted or unsubstituted 2-(dimethylamino)-5-pyrimidinecarboxylates 10-20, which is mainly carried out by reaction of ethyl or methyl 2-[(dimethylamino)methylene]-3- oxoalkanoates with 1,1-dimethylguanidine, is described. The above esters were hydrolyzed to the relative carboxylic acids 21-30, which were decarboxylated to the corresponding 2,4-disubstituted pyrimidines 31-40. All the new synthesized pyrimidines were evaluated in spontaneously beating and electrically driven atria from reserpine-treated guinea pigs. Their effects were compared to those induced by milrinone in both atria preparations. Compound 28 (4-benzyl-2-(dimethylamino)-5-pyrimidinecarboxylic acid) was the most effective positive inotropic agent, while the corresponding methyl ester 17 reduced both the contractile force and the frequency of guinea pig atria. An antagonism toward the negative influence exerted by endogenous adenosine on the heart seems to be involved in the contractile activity of compound 28. By contrast, compound 17 might be partial agonist at the purinergic inhibitory (A1) receptor. X-ray analysis carried out on 17 and 28 and molecular modeling investigations extended also to related derivatives allowed a possible rationalization between structure and inotropic activity for this series of compounds.

L37 ANSWER 24 OF 35 MEDLINE on STN
ACCESSION NUMBER: 94046963 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8230117
TITLE: The crystal structure, absolute configuration, and phosphodiesterase inhibitory activity of (+)-1-(4-bromobenzyl)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)-pyrrolidin-2-one.
AUTHOR: Baures P W; Eggleston D S; Erhard K F; Cieslinski L B; Torphy T J; Christensen S B
CORPORATE SOURCE: Department of Physical and Structural Chemistry, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406-0939.
SOURCE: Journal of medicinal chemistry, (1993 Oct 29) Vol. 36, No. 22, pp. 3274-7.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Mar 2000
Entered Medline: 10 Dec 1993

AB Chiral HPLC resolution of the phosphodiesterase IV (PDE IV) inhibitor rolipram (1) provided (-)-1, and this enantiomer was converted into its 1-(4-bromobenzyl) derivative, (+)-2. X-ray structural analysis of (+)-2 established the absolute configuration as R, which provides the first direct evidence for a previously assumed assignment of configuration. The crystal structure of (+)-2 and the PDE inhibitory activity of both enantiomers of 2 are discussed in the context of a previously proposed topological model.

L37 ANSWER 25 OF 35 MEDLINE on STN
ACCESSION NUMBER: 94092979 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8268438
TITLE: Role of ischemia-reperfusion on myocardial cyclic AMP and cyclic AMP phosphodiesterase: effects of amrinone on regional myocardial force and shortening.
AUTHOR: Tse J; Cimini C; Kedem J; Rodriquez E; Gonzalez M; Weiss H R
CORPORATE SOURCE: Department of Anesthesia Physiology and Biophysics, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick 08903-0019.
SOURCE: Journal of cardiothoracic and vascular anesthesia, (1993 Oct) Vol. 7, No. 5, pp. 566-72.

Journal code: 9110208. ISSN: 1053-0770.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 15 Feb 1994
Last Updated on STN: 15 Feb 1994
Entered Medline: 31 Jan 1994

AB This study tested the hypothesis that a reperfused ischemic myocardial region of the dog heart would be unable to increase its function in response to amrinone, a specific cyclic AMP phosphodiesterase (cAMP-PDE) inhibitor, due to loss of cAMP-PDE activity in the region. The global contractility (+dp/dtmax), regional percent shortening (ultrasonic crystals), and developed force (miniature force gauge) were measured on a continuous basis throughout a 6-hour experiment and regional blood flow (radioactive microspheres) in open-chest pentobarbital- anesthetized mongrel dogs. The left anterior descending coronary artery (LAD) was isolated and ligated for 2 hours and allowed to reperfuse for 4 hours. This myocardial region was compared to a nonischemic region supplied by the circumflex artery. At the end of the 4-hour reperfusion period, 9 dogs were treated with amrinone (5 mg/kg) and three dogs were not treated with amrinone. The hearts were rapidly excised and frozen in liquid nitrogen. Cyclic AMP and cAMP-PDE activity was determined in homogenates of myocardial tissue. Blood flow decreased during occlusion in the LAD region and returned toward control with reperfusion. Flow increased nonsignificantly with amrinone. the basal cyclic AMP content of the two regions was not different. The cAMP-PDE activity was reduced 24% in the LAD region compared to the control region. There were no ischemia-induced changes in the enzyme characteristics. These experiments demonstrated increased global function in the ischemic reperfused myocardium after amrinone was administered (dP/dtmax: 2092 +/- 538 to 3277 +/- 688 mmHg/sec).(ABSTRACT TRUNCATED AT 250 WORDS)

L37 ANSWER 26 OF 35 MEDLINE on STN
ACCESSION NUMBER: 92378785 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1369389
TITLE: Jatropham derivatives and steroidal saponins from the bulbs of Lilium hansonii.
AUTHOR: Ori K; Mimaki Y; Mito K; Sashida Y; Nikaido T; Ohmoto T; Masuko A
CORPORATE SOURCE: Tokyo College of Pharmacy, Japan.
SOURCE: Phytochemistry, (1992 Aug) Vol. 31, No. 8, pp. 2767-75. Journal code: 0151434. ISSN: 0031-9422.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Biotechnology
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 9 Aug 1995
Last Updated on STN: 9 Aug 1995
Entered Medline: 30 Sep 1992

AB Two new jatropham derivatives and three new steroidal saponins were isolated from the fresh bulbs of Lilium hansonii, along with previously known compounds. The structures of the new compounds were elucidated, on the basis of spectroscopic data and chemical evidence, and by comparing them with those of known compounds, as (-)-5-hydroxy-3-methyl-3-pyrrolin-2- one (jatropham) 5-O-beta-D-glucopyranosyl-(1----3)-beta-D-glucopyranoside, (2S*,4R*)-1-(3-methyl-2-oxo-3-pyrrolinyl)-4-methyl-5-oxo-2-pyrr olidinecarboxyli c acid, 26-O-beta-D-glucopyranosyl-(25R)-5 alpha-furostan-3 beta,22 zeta-diol 3-O-alpha-L-rhamnopyranosyl-(1----2)-O- [beta-D-glucopyranosyl-(1----4)]- beta-D-glucopyranoside, (25R)-5 alpha-spirostan-3 beta,12 alpha-diol 3-O-alpha-L-rhamnopyranosyl-(1----2)- O-[beta-D-glucopyranosyl-(1----4)]- beta-D-glucopyranoside and (25R)-spirost-5-en-3 beta,12 alpha-diol 3-O-alpha-L-rhamnopyranosyl-(1---- 2)-O-[beta-D-glucopyranosyl-(1----4)]- beta-D-glucopyranoside, respectively. The stereostructure of jatropham dimer, the plain structure of which was presented previously, was confirmed by X- ray crystallographic analysis. The inhibitory activity on cyclic AMP phosphodiesterase of the steroidal saponins was evaluated.

L37 ANSWER 27 OF 35 MEDLINE on STN
ACCESSION NUMBER: 88035915 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2822927
TITLE: Cardiotonic agents. 8. Selective inhibitors of adenosine 3',5'-cyclic phosphate phosphodiesterase III. Elaboration of a five-point model for positive inotropic activity.

AUTHOR: Moos W H; Humblet C C; Sircar I; Rithner C; Weishaar R E; Bristol J A; McPhail A T
CORPORATE SOURCE: Department of Chemistry, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.
SOURCE: Journal of medicinal chemistry, (1987 Nov) Vol. 30, No. 11, pp. 1963-72.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712
ENTRY DATE: Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 9 Dec 1987

AB Inhibitors of adenosine 3',5'-cyclic phosphate phosphodiesterase III (cAMP PDE III) were studied by using solid-state, solution, and theoretical methods in order to refine a five-point model for positive inotropic activity. Cyclic AMP PDE III inhibitors bear a striking resemblance to cAMP itself. This investigation supports the importance of an overall planar topography for selective and potent cAMP PDE III inhibition. (Possible reasons for the potency of certain nonplanar compounds are discussed.) Cardiotonics like imazodan (1; CI-914) and 2 (CI-930) can readily achieve essentially planar geometries, as shown with X- ray crystallographic, IR, UV, NMR, and theoretical data. Small alkyl substituents that occupy space corresponding to certain portions of the cAMP sugar region increase potency (see, e.g., 2, 4). Selective inhibition of cAMP PDE III can be achieved by mimicking the attractive electrostatic potential associated with the phosphate group (e.g., with an amide) and by providing an additional attractive potential spatially opposite to the previous one, in the vicinity of the adenine N1 and extending to N3 (e.g., with an imidazole), together with a partial dipole moment comparable to the adenine dipole moment. This extends and better defines our five-point model in terms of cAMP, a natural substrate for PDE.

L37 ANSWER 28 OF 35 MEDLINE on STN
ACCESSION NUMBER: 87169585 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3031290
TITLE: Molecular structure of the dihydropyridazinone cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-pyridazinyl)- 2H-indol-2-one, a potent inhibitor of cyclic AMP phosphodiesterase.
AUTHOR: Robertson D W; Jones N D; Krushinski J H; Pollock G D; Swartzendruber J K; Hayes J S
SOURCE: Journal of medicinal chemistry, (1987 Apr) Vol. 30, No. 4, pp. 623-7.
Journal code: 9716531. ISSN: 0022-2623.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198705
ENTRY DATE: Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 1990
Entered Medline: 11 May 1987

AB The cardiotonic 1,3-dihydro-3,3-dimethyl-5-(1,4,5,6-tetrahydro-6-oxo-3- pyridazinyl)-2H-indol-2-one (1, LY195115) is a potent, competitive inhibitor (Ki = 80 nM) of sarcoplasmic reticulum derived phosphodiesterase (SR-PDE). Moreover, the compound is a potent positive inotrope both in vitro and in vivo. To assist further cardiotonic drug-design studies, we have mapped the three-dimensional structure of 1 using X- ray crystallography. From a global viewpoint, this drug was essentially planar, but two small regions of nonplanarity were apparent. These involved the geminal methyl substituents in the indol-2-one moiety and the C5' methylene unit of the dihydropyridazinone ring. Because of our previous studies involving the bipyridine cardiotonics amrinone and milrinone, the conformational relationship between the plane of the phenyl ring and the horizontal symmetry plane defined by N2', C3', and C4' of 1 was of particular interest. The C6-C5-C3'-C4' dihedral angle was -2.7 degrees, whereas the C6-C5-C3'-N2' dihedral angle was 174.6 degrees. Therefore the two rings maintain a high degree of coplanarity. Compound 4, the congener of 1 possessing a completely unsaturated pyridazinone ring was also studied. In terms of inotropic activity, this compound, devoid of any puckering in the pyridazinone moiety, was equipotent with 1. Methyl substitution at the 4-position of the dihydropyridazinone and pyridazinone rings provided disparate results. Compound 2, the 4-methyl analogue of 1,

was 2-fold more potent than 1, and the methyl substituent probably caused only minor perturbations in overall molecular topology. However 5, the 4-methyl analogue of the pyridazinone 4, was 4.4-fold less active than 4, perhaps as a result of methyl-induced molecular nonplanarity.

L37 ANSWER 29 OF 35 MEDLINE on STN
ACCESSION NUMBER: 85288595 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2993219
TITLE: Griseolic acid, an inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase. II. The structure of griseolic acid.
AUTHOR: Takahashi S; Nakagawa F; Kawazoe K; Furukawa Y; Sato S; Tamura C; Naito A
SOURCE: The Journal of antibiotics, (1985 Jul) Vol. 38, No. 7, pp. 830-4.
Journal code: 0151115. ISSN: 0021-8820.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198510
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 23 Oct 1985
AB Griseolic acid, a potent inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase, was isolated from the fermentation broth of Streptomyces griseoaurantiacus SANK 63479. Treatment of griseolic acid with HCl-MeOH gave adenine and pseudo-sugar. The structure of griseolic acid, adenine nucleoside type structure, was elucidated by chemical degradation and X-ray analysis, and was shown to be structure 1.

L37 ANSWER 30 OF 35 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 84135414 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6321422
TITLE: Terferol, an inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase. II. Structural elucidation.
AUTHOR: Nakagawa F; Takahashi S; Naito A; Sato S; Iwabuchi S; Tamura C
SOURCE: The Journal of antibiotics, (1984 Jan) Vol. 37, No. 1, pp. 10-2.
Journal code: 0151115. ISSN: 0021-8820.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198404
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 19 Mar 1990
Entered Medline: 24 Apr 1984
AB Streptomyces showdoensis SANK 65080 produced terferol, an inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase (cAMP-PDE). NMR spectrometry and X-ray analysis were used to determine the structure of the compound, a new member of the terphenyl family.

L37 ANSWER 31 OF 35 MEDLINE on STN
ACCESSION NUMBER: 78202874 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 208095
TITLE: Cyclic nucleotide changes in X-irradiated synchronized Tetrahymena.
AUTHOR: Charp P A; Whitson G L
SOURCE: Radiation research, (1978 May) Vol. 74, No. 2, pp. 323-34.
Journal code: 0401245. ISSN: 0033-7587.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 197808
ENTRY DATE: Entered STN: 14 Mar 1990

Last Updated on STN: 14 Mar 1990
Entered Medline: 28 Aug 1978

L37 ANSWER 32 OF 35 MEDLINE on STN
ACCESSION NUMBER: 77161677 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 192526
TITLE: [Effect of ionizing radiation on the activity of adenylate cyclase, cAMP phosphodiesterase and the level of cAMP in mouse liver].
O vliianii ioniziruiushchei radiatsii na aktivnost' adenilattsiklazy, fosfodiesterazy tsAMF i uroven'tsAMF v pecheni myshei.
AUTHOR: Sobolev A S; Orekhov A N; Chirkov Iu Iu; Tertov V V; Kudriashov Iu B
SOURCE: Doklady Akademii nauk SSSR, (1977) Vol. 232, No. 6, pp. 1445-7.
Journal code: 7505465. ISSN: 0002-3264.
PUB. COUNTRY: USSR
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197706
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 22 Jun 1977

L37 ANSWER 33 OF 35 MEDLINE on STN
ACCESSION NUMBER: 78019973 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 20895
TITLE: Adenosine 3' , 5'-cyclic monophsphate phosphodiesterase activities in the x-irradiation induced rat small bowel adenocarcinoma.
AUTHOR: Lawson A J; Wall D D; Osborne J W; Stevens R H
SOURCE: Biochemical and biophysical research communications, (1977 Oct 10) Vol. 78, No. 3, pp. 992-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197711
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 30 Nov 1977

L37 ANSWER 34 OF 35 MEDLINE on STN
ACCESSION NUMBER: 76066119 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 172331
TITLE: The 3'-amido and 5'-amido analogues of adenosine 3':5'-monophosphate; interaction with cAMP-specific proteins.
AUTHOR: Panitz N; Rieke E; Morr M; Wagner K G; Roesler G; Jastorff B
SOURCE: European journal of biochemistry / FEBS, (1975 Jul 1) Vol. 55, No. 2, pp. 415-22.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197603
ENTRY DATE: Entered STN: 13 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 1 Mar 1976

AB The sensitivity for recognition of adenosine 3:5'-monophosphate (cAMP) by its coordinate proteins towards chemical changes in the six-membered cyclic phosphate ring has been investigated. A comparison of the interaction parameters of the 3' and 5'-amido analogues (I, II) and of unsubstituted cAMP has been made using two different protein kinases and the phosphodiesterase from bovine heart. Binding affinity and the capacity of the amido analogues to stimulate the phosphotransferase activity of the kinases is greatly reeuced relative to cAMP, the 3'-position being more sensitive towards the modification than the

5'-position. The coordinate noncyclic derivatives, 3'-deoxy-3'-amino-5'- AMP (IV) and 5'-deoxy-5'-amino-3'-amp (iii), were also tested. Surprisingly activity towards protein kinases was found to be considerable for the 5'-deoxy-5'-amino-3'-AMP (III), while the 3'-deoxy-3'-amino-5'-AMP (IV) is practically inactive. A possible reason for this is that the noncylic 5'-analogue (III) may be able to assume a cyclic structure maintained by internal salt formation. The phosphodiesterase splits both cyclic amido analogues but with reduced rates compared to that of natural cAMP. Kinetic data obtained from different methods reveal a stronger affinity for the 5'-analogue (I) than the 3'-analogue (II) for the active site, although the reaction rate at saturated substrate concentration is significantly higher with II than with I. The properties of the amido and the noncyclic amino analogues are discussed with available data from chemotaxis of the cellular slime moulds. Furthermore data of the respective methylene cyclic derivatives are used for a more comprehensive comparison. The above is interpreted in terms of the electronic features of the substitutions and of the changes in bond distances or angles upon replacement of O by NH or CH2 in the cyclic phosphate ring (obtained from X-ray work).

L37 ANSWER 35 OF 35 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1975:55703 CAPLUS Full-text
DOCUMENT NUMBER: 82:55703
TITLE: Hydrolysis of adenosine cyclic 2',3'-monophosphate and adenosine cyclic 3',5'-monophosphate in subcellular fractions of normal and neoplastic mouse spleen
AUTHOR(S): Kohings, Antonius W. T.; Pierce, David A.
CORPORATE SOURCE: Lab. Radiopathol., State Univ. Groningen, Groningen, Neth.
SOURCE: Life Sciences (1974), 15(3), 491-9
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A comparison was made of capacity of subcellular fractions of normal and neoplastic (lymphosarcoma) spleen of C57BL mice to hydrolyze adenosine cyclic 2',3'-monophosphate and adenosine cyclic 3',5'-monophosphate. The 2',3'-cyclic nucleotide phosphodiesterase (I) had highest activity in the particulate fraction of the cell whereas the 3',5'- cyclic nucleotide phosphodiesterase (II) had highest activity in the soluble fraction. I activity was higher in tumor tissue than normal tissue, whereas II activity was higher in normal tissue. Total body irradiation of normal mice with 600 rads of X- ray resulted in a drop of I activity 48 hr after exposure, whereas II was unaffected. Imidazol or Mg2+ had no effect on I. The pH optima for I and II were 6.2 and 7.7, resp. The 2 enzymes are probably not identical in mouse spleen.

=> log y